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Neuroticism and common mental disorders: Meaning and utility of a complex relationship

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HIGHLIGHTS

- Neuroticism (N) predicts common mental disorders (CMDs) but confounding is substantial.
- Five models have been proposed to explain the prospective N-CMD association.
- The most explanatory models are common cause, spectrum, and vulnerability model.
- N is etiologically not very informative but an easy marker of non-specified general risk.
- We need to establish whether interventions targeting neuroticism reduce CMD risk.

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ABSTRACT

Neuroticism's prospective association with common mental disorders (CMDs) has fueled the assumption that neuroticism is an independent etiologically informative risk factor. This *vulnerability* model postulates that neuroticism sets in motion processes that lead to CMDs. However, four other models seek to explain the association, including the *spectrum* model (manifestations of the same process), *common cause* model (shared determinants), *state* and *scar* models (CMD episode adds temporary/permanent neuroticism). To examine their validity we reviewed literature on confounding, operational overlap, stability and change, determinants, and treatment effects. None of the models is able to account for (virtually) all findings. The state and scar model cannot explain the prospective association. The spectrum model has some relevance, especially for internalizing disorders. Common causes are most important but the vulnerability model cannot be excluded although confounding of the prospective association by baseline symptoms and psychiatric history is substantial. In fact, some of the findings, such as interactions with stress and the small decay of neuroticism's effect over time, are consistent with the vulnerability model. We describe research designs that discriminate the remaining models and plea for deconstruction of neuroticism. Neuroticism is etiologically not informative yet but useful as an efficient marker of *non-specified* general risk.

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1. Introduction

The broad personality trait of neuroticism is strongly associated with Axis I psychopathology, in particular the common mental disorders (CMDs), including anxiety, mood, and substance use disorders (e.g. Clark, Watson, & Mineka, 1994; Kotov, Gamez, Schmidt, & Watson, 2010; Lahey, 2009; Malouff, Thorsteinsson, & Schutte, 2005; Ormel, Oldehinkel, & Brilman, 2001; Ormel & Wohlfarth, 1991; Ruiz, Pincus, & Schinka, 2008). Very recently an important meta-analysis quantified neuroticism's cross-sectional association with CMDs, ranging in magnitude from Cohen's *d* of 0.5 for substance disorders, to 2.0 for some anxiety and mood disorders (Kotov et al., 2010). Neuroticism is also the single strongest predictor of CMDs although the prospective association is typically weaker compared to the cross-sectional association (de Graaf, Bijl, Ravelli, Smit, & Vollebergh, 2002; Lahey, 2009; Ormel, Rosmalen, & Farmer, 2004). Neuroticism also plays an important role in other phenomena that correlate strongly with psychological distress, e.g. persistent low subjective well-being, and physical health problems (Costa & McCrae, 1980; Duncan-Jones, Fergusson, Ormel, & Horwood, 1990; Heller, Watson, & Ilies, 2004; Watson, 2000). Neuroticism is also associated with important outcomes like occupational attainment, divorce, and mortality (Lahey, 2009; Roberts, Kuncel, Shiner, Caspi, & Goldberg, 2007). Furthermore, neuroticism accounts for a substantial proportion of current and lifetime comorbidity, most strongly within the domain of internalizing disorders, but also between internalizing and externalizing problems (Clark, 2005; Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Watson, Kotov, & Gamez, 2006), and between mental and physical illness (Neeleman, Bijl, & Ormel, 2004; Neeleman, Ormel, & Bijl, 2001).

Five fundamental theories have been proposed to explain the neuroticism–CMDs link (Caspi, Roberts, & Shiner, 2005; Clark, 2005; Klein, Kotov, & Bufferd, 2011; Krueger & Tackett, 2003; Ormel, Oldehinkel, & Vollebergh, 2004; Widiger, Verheul, & van den Brink, 1999). (1) The *vulnerability* model postulates that neuroticism sets in motion processes that lead to CMDs, i.e. high neuroticism either causes the development of CMDs directly or enhances the impact of causal risk factors such as stressful life events (e.g., diathesis-stress scenario). Examples of such processes are a negative bias in attention, interpretation and recall of information, increased reactivity, and ineffective coping. (2) The *spectrum* model is based on the assumption that neuroticism and CMDs are different manifestations of the same processes, with CMDs representing the high ends of continuously distributed neuroticism. The spectrum model considers high neuroticism scores as equivalent to symptoms of CMD. (3) According to the *common cause* model is neuroticism predictive for CMDs because the two constructs share genetic and environmental determinants. Shared roots produce non-causal statistical associations between the two. (4) The *scar* model proposes that neuroticism is shaped by CMDs, in that the experience of a major CMD episode has permanent effects on neuroticism, thus persisting after the episode has remitted. Finally, (5) the *state* model also asserts that neuroticism is shaped by CMDs but, in contrast with the scar model, argues that the effects of CMDs are temporary and disappear after the episode has remitted. It is important to note that the models are not mutually exclusive and that the borders between them are blurry. Table 1 describes specific predictions of each model, divided into necessary conditions (model is incorrect if condition is not met) and supportive

Table 1
Empirical implications of fundamental models of the relationship between neuroticism and common mental disorders (CMDs).

Models	Necessary condition	Supportive evidence
Vulnerability	1) Prospective association, i.e. neuroticism predicts first-ever episode of any CMD after adjustment for baseline symptoms 2) Neuroticism interacts with environmental determinants (e.g., life stress) to produce CMD	1) Presence of a clearly explicated causal chain linking neuroticism to CMD onset 2) Neuroticism mediates effect of psychological treatment on reduction of CMD symptoms
Common cause	1) Common determinants (assessed concurrently or prior to personality) account for the association between neuroticism and CMD	Primary prevention of CMD does also reduce neuroticism, in excess of the state effect.
Spectrum	1) Strong and specific association between neuroticism and CMD 2) Neuroticism and CMD share determinants 3) Overlap in measurement content	1) Synchrony of change in neuroticism and CMD symptoms 2) Similar differential stability 3) Treatment is equally effective in reducing symptoms and neuroticism scores
Scar	Post-episode neuroticism higher than pre-episode neuroticism	
State	1) Cross-sectional association 2) Effective treatment of CMD reduces neuroticism 3) Synchrony of change in neuroticism and CMD severity	1) Prospective association

Note. Necessary condition indicates that model is incorrect if condition is not met. Supportive evidence is consistent with the model but their absence does not invalidate the model.

evidence (consistent with the model but absence does not invalidate the model).

The objective of the current paper is to evaluate available evidence bearing on the validity of these models. It is in particular the prospective association linking baseline neuroticism to later CMDs that has encouraged many to consider neuroticism a robust independent and etiologically informative risk factor of CMDs, e.g. (Fanous, Neale, Aggen, & Kendler, 2007; Kendler & Prescott, 2006; Khan et al., 2005; Krueger, Caspi, Moffitt, Silva, & McGee, 1996; Lahey, 2009; Ormel & Wohlfarth, 1991; Ormel et al., 2001; van Os, Park, & Jones, 2001; Vink et al., 2009). However, this preference for the vulnerability model may be premature given that research to date has neither critically examined the vulnerability model nor sufficiently evaluated the validity of competing models.

To examine the validity of the models we examined the evidence on the following topics: the prospective association between neuroticism and CMDs; item overlap between measures of neuroticism and CMDs; the extent to which neuroticism and CMDs share determinants; differential change and stability of neuroticism and psychiatric symptoms and disorders, and treatment effects on neuroticism and CMDs. To identify studies examining the prospective association between neuroticism and later axis-1 psychopathology, we searched the Web of Knowledge. This yielded 418 studies, of which 46 met our inclusion criteria.

The present work extends earlier work on cross-sectional associations to a critical evaluation of explanatory models of the prospective association. Three other broad personality traits, low Conscientiousness, Disinhibition, and Extraversion, have often been linked to CMDs as well, but their association with CMDs is not as strong and pervasive as that of neuroticism (Clark, 2005; Fanous et al., 2007; Khan et al., 2005; Klein et al., 2011; Kotov et al., 2010; Malouff et al., 2005). Analyses of these traits are outside the scope of this review, but we believe that the implications of our findings on neuroticism are relevant for understanding the relationship between other personality traits and CMDs as well. First we address briefly the definition and measurement of both neuroticism and CMDs.

2. Definition and measurement of neuroticism

Neuroticism is one of the broad traits at the apex of personality taxonomy. The term neuroticism has its roots in Freudian theory. The modern concept of neuroticism was introduced by Hans Eysenck and others using a range of methods from personality psychology, including psychophysiological and lexical studies (Eysenck, 1967; Eysenck & Eysenck, 1985; John, Robins, & Pervin, 2008; Mathews, Fox, Yiend, & Calder, 2003; Pervin & John, 1999; Widiger, Hurt, Frances, Clarkin, & Gilmore, 1984). The lexical model assumes that language represents what is of most importance, interest, or meaning to individuals (Goldberg, Bridges, Cook, Evans, & Grayson, 1990; Matthews, Deary, & Whiteman, 2003; Pervin & John, 1999). Eysenck and others referred to neuroticism as a trait of emotionality, specifically the tendency to arouse quickly when stimulated and to inhibit emotions slowly (Eysenck & Eysenck, 1985). Costa and McCrae defined neuroticism as a dimension of maladjustment or negative emotionality versus adjustment and emotional stability (Costa & McCrae, 1992). Others have emphasized possible etiological components of neuroticism; such as an inability to control urges; inefficient coping with stress; a preference for preemptive threat management strategies; a disposition to complain; or the tendency to have unrealistic ideas, appraise situations as stressful, and experience aversive emotional states. Differences among definitions have been reconciled in the late 1990s with the consensus definition that, at its core, neuroticism is the propensity to experience negative emotions (Clark & Watson, 1999; Depue & Lenzenweger, 2001; Digman, 1997; Matthews et al., 2003; McCrae & Costa, 1997; Tellegen & Waller, 1997; Widiger, 2009).

Self-report questionnaires are the most common methods of personality assessment, followed by report by others who know the index person well, such as peers and parents. Objective behavioral tests have shown to correlate only weakly with personality questionnaires, in part because laboratory tests have difficulty capturing broad constructs like neuroticism (John et al., 2008; Mathews et al., 2003; Pervin & John, 1999; Widiger et al., 1984).

Although modern measures of neuroticism are based on the same core construct, they show differences with regard to its facets or lower-order traits (Pervin & John, 1999). While Anxiety-Withdrawal, Depression-Unhappiness, Vulnerability-Stress Reaction are typically considered facets of neuroticism, there is less agreement whether Angry Hostility-Aggression, Impulsivity, Inferiority, and Dependency belong to the neuroticism domain.

3. Definition and measurement of common mental disorders (CMDs)

Two widely used modern classifications of mental disorders are the Diagnostic Statistical Manual 4th edition (DSM-IV) and the International Classification of Diseases (ICD-10) (Kaplan & Sadock, 1995). Therein mental disorders are defined as a clinically significant behavioral or psychological syndrome or pattern that occurs in a person and associates with present distress (a painful symptom) or disability (impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom (American Psychiatric Association, 1994). The symptoms must also not be a normal and expectable response to a particular event (e.g. sadness after the death of a loved one) but out of proportion. Whatever its original causes, the symptoms must be considered a manifestation of a behavioral, psychological, or biological dysfunction in the person. Both classifications describe a large number of mental disorders by means of operational definitions based as much as possible on empirical phenotypic criteria. This has improved the reliability of diagnoses and their use in clinical practice and research. The operational criteria have also led to reliable interview-based diagnostic interviews and self-report symptom measures (Tsuang & Tohen, 2002). However, the existence of substantial comorbidity and heterogeneity in etiology and treatment effects within the very same disorder suggests that the validity of the classifications and their fine distinctions is far from optimal. It is expected that, with increasing etiological knowledge, future classifications will become more etiologically based.

Efforts to examine the structure of psychopathology have resulted in the distinction of internalizing (tendency to express distress inwards) versus externalizing (tendency to express distress outwards) disorders (Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh et al., 2001). Three classes of mental disorders are especially common in the general population: anxiety, depressive, and substance use disorders. Anxiety disorders typically include panic disorder, social anxiety disorder, specific phobia, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, and separation anxiety disorder. Depressive disorders include major depressive disorder, major depressive episodes and dysthymia. Substance use disorders typically include alcohol abuse/dependence and drug abuse/dependence. The 18-country Collaborative WHO World Mental Health Surveys reported inter-quartile lifetime prevalence estimates ranging from 9.9 to 16.7 for any anxiety disorder, from 9.8 to 15.8 for any depressive disorder, and from 4.8 to 9.6 for any substance use disorder (Kessler et al., 2007). The anxiety and depressive disorders are part of the internalizing domain, which also includes somatoform disorders. The substance-use disorders are part of the externalizing domain, together with conduct and impulse control disorders, and — according to some models — attention deficit and hyperactivity disorders (ADHD). Our review focuses on neuroticism's relationship with these three classes of common mental disorders which we collectively denote as CMDs

in this paper. Thus, we do not review relatively common mental disorders from other classes such as ADHD and conduct disorder.

4. Associations between neuroticism and common mental disorders

4.1. Cross-sectional studies

Recently, Kotov et al. (2010) performed a quantitative review of cross-sectional associations between six higher order personality traits, including neuroticism, and 11 mental disorders, including the CMDs disorders. All diagnostic groups were high on neuroticism (mean Cohen's $d = 1.65$). As a heuristic to guide interpretation of findings, *d*'s from 0.20 to 0.40 conventionally indicate a small effect, 0.41–0.79 a medium effect, and 0.80+ a large effect. Anxiety disorders showed the strongest link with neuroticism (e.g. panic disorder: $d = 1.92$), closely followed by depressive disorders (e.g. major depressive disorder: $d = 1.33$). Neuroticism's link with substance use disorders was considerably lower (e.g. alcohol abuse: $d = 0.77$). Moderator analyses indicated that epidemiologic samples produced smaller effects than patient samples and that Eysenck's inventories showed weaker associations than NEO scales. While neuroticism was by far the strongest correlate of most CMDs, several other traits showed substantial associations independent of neuroticism.

4.2. Prospective studies

We searched the Web of Knowledge in May 2012 for prospective studies linking neuroticism to later CMDs. We used search strings that combined terms from the following three sets: (a) neuroticism, trait anxiety or negative affectivity; (b) mental disorder, internalizing disorder, externalizing disorder, anxiety disorder, mood disorder, psychopathology or mental health/illness; and (c) longitudinal, prospective or follow-up. This yielded 418 studies, of which 46 met our inclusion criteria (Jeronimus, Kotov, Riese and Ormel: The prospective relationship between neuroticism and psychopathology: A meta-analysis. 2013. Unpublished manuscript, available on request). To be included, a study must have (a) an adult sample that was at least 18 years at follow-up (b) from the general population (c) of at least 200 participants, (d) with assessment of neuroticism at baseline and (e) assessment of axis-1 psychopathology at a follow-up at least one year after the baseline. We excluded studies that (a) comprised patient groups (mental/somatic) or prisoners, (b) did not report information necessary to calculate sample size or effect sizes, or (c) did not include one or more CMDs as defined above. We were particularly interested in studies that measured not only neuroticism, but also psychopathology at baseline, because these studies could correct for confounding due to baseline psychopathology in the neuroticism-psychopathology association. For example, some studies excluded subjects with a previous or current axis-1 diagnosis, or adjusted the association for baseline psychiatric symptoms, or both.

Tables 2 and 3 present summary statistics which we composed using the information retrieved by Jeronimus and colleagues (2013). The tables distinguish four categories of disorders: (a) anxiety (PTSD, panic disorder, GAD, and the phobic disorders including social anxiety disorder); (b) depression, including suicide and dysthymia; (c) substance abuse, such as illicit drugs, alcohol and tobacco; and (d) psychological distress (the meta-analysis also include other disorders than these four categories).[2]

[2] Because studies differed in terms of (i) the metric of predictor (neuroticism) and outcome (psychopathology) variables (ranging from dichotomies to continuous variables) and (ii) the statistic used to estimate the magnitude of the association, Jeronimus and colleagues converted study findings into a common metric (Cohen's *d*) (Borenstein, 2009). Hazard ratios are not convertible to other effect sizes, and hence 4 studies are not included in Tables 2 and 3.

Table 2
Summary of predictive effects of neuroticism as sample-size weighted effect-sizes *d* over K studies and N participants.

Disorder		Symptoms				Diagnosis			
		K	N	*d*	SD*d*	K	N	*d*	SD*d*
Anxiety	Unadjusted	8	9820	0.69	0.40	2	6579	0.52	0.32
	Adjusted	6	6104	0.37	0.32	6	13,073	0.18	0.11
Depression	Unadjusted	11	13,379	0.74	0.37	10	37,992	0.49	0.28
	Adjusted	4	2876	0.33	0.14	13	45,522	0.32	0.36
Substance use	Unadjusted	3	5654	0.30	0.09	3	10,204	0.22	0.17
	Adjusted	1	961	0.28		5	14,826	0.21	0.24
Psychological distress	Unadjusted	3	1723	0.87	0.87	1	3625	0.48	
	Adjusted	3	4804	0.27	0.24	1	968	0.12	

Legend: K = number of studies, N = pooled sample size, *d* = sample size-weighted average effect size, SD*d* = sample size-weighted standard deviation of effect sizes. For details, see Jeronimus et al., in press.

The pool of studies is quite heterogeneous, as indicated by rather large SDs around averages. Despite the variability, the data in Table 2 clearly support the ability of neuroticism to predict CMDs, especially for internalizing symptoms and disorders and psychological distress (mean $d = 0.63$, range 0.48–0.87). The association with substance use symptoms and disorders is considerably weaker ($d = 0.26$). The estimated unadjusted prospective associations between neuroticism and CMDs are about half the meta-analytic estimates of the cross-sectional associations reported by Kotov et al. (2010). We reanalyzed Kotov's et al. data to be as comparable to the data reported in the current study. Specifically, we included only epidemiological studies, removed attenuation for unreliability, and selected only common mental disorders. Then, the comparison of cross-sectional studies versus prospective studies comes out as 1.08 versus 0.52 for anxiety, 0.86 versus 0.49 for depression, and 0.52 versus 0.22 for substance disorders. The difference in effect size between prospective and cross-sectional studies suggests that about half of the cross-sectional association is due to relations with mental state, which is *in*consistent with the vulnerability model but in line with the state and the spectrum models and neutral with regard the common cause model.

Neuroticism's associations with symptom measures based on self-ratings are typically stronger than for diagnoses (Table 2). Diagnoses are typically based on diagnostic interviews. For unadjusted effect sizes, the difference amounts to $d = 0.18$ (0.58 versus 0.41). This suggests the existence of method variance, as both neuroticism and symptom measures are typically assessed with self-ratings, whereas diagnostic interviews are based on self-report in response to interviewer questions. Unfortunately, it is not possible to establish the extent of method variance in the observed prospective associations with diagnoses.

Table 3
Summary of predictive effects of neuroticism as sample-size weighted effect sizes *d* over K studies and N participants, for short versus long time intervals.

	Symptoms				Diagnosis			
	K	N	*d*	SD*d*	K	N	*d*	SD*d*
Unadjusted	16	20,461	0.63	0.35	10	37,992	0.47	0.25
Short interval	7	9095	0.67	0.34	6	26,535	0.47	0.25
Long interval	9	11,366	0.60	0.37	4	11,457	0.47	0.17
Adjusted	8	7553	0.35	0.30	15	50,900	0.30	0.34
Short interval	6	4759	0.48	0.40	9	17,700	0.31	0.29
Long interval	2	2794	0.14	0.02	6	33,200	0.29	0.29

K = number of studies, N = pooled sample size, *d* = sample size-weighted average effect size, SD*d* = sample size-weighted standard deviation of effect sizes. The division of studies over short and long intervals was based on the median follow-up time, for both symptoms and diagnosis 3 years. For details, see Jeronimus et al., in press.

4.3. Adjusting for psychiatric confounders

A strong test of the vulnerability model is one that evaluates the ability of neuroticism to predict onset of a given disorder while adjusting for all baseline psychiatric symptoms, i.e. the symptoms present at the time the study assessed neuroticism, and earlier episodes of CMDs as well (Jeronimus et al., in press). Control for baseline symptoms is important because of the robust evidence of the state component in neuroticism; control for earlier episodes is important because earlier episodes may have left scars expressed as increased neuroticism. Although support for the scar model is inconsistent and virtually limited to major depression, with some evidence in favor (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Rohde, Lewinsohn, & Seeley, 1994) and some against it (Ormel, Oldehinkel & Vollebergh, 2004; Rohde, Lewinsohn, & Seeley, 1990; Shea et al., 1996), long-term effects of remitted episodes on neuroticism cannot be ruled out.

The adjusted effect sizes regarding internalizing symptoms and disorders dropped on average with 51% compared to their unadjusted counterparts (from $d = 0.53$ to $d = 0.26$). This substantial drop is consistent with the spectrum model. However, the weak residual prospective association supports the vulnerability model. This drop is also consistent with the common cause model. The drop was most marked for anxiety disorders and psychological distress, suggesting that these outcomes are most sensitive to confounding by baseline psychiatric symptoms (see also next section). The weak prospective association of neuroticism with substance use was not affected by adjustment, supporting the vulnerability model for substance use disorders.

Jeronimus and colleagues (Jeronimus et al., in press) did not find a single study that controlled for all relevant baseline symptoms and earlier episodes. Nevertheless, three studies came close to comprehensive control. Two still found significant predictive effects (de Graaf et al., 2002; Krueger, 1999) and one did not (Engelhard, van den Hout, & Kindt, 2003). The largest of these studies (n = 7076, age 18–64) (de Graaf et al., 2002) investigated the association between baseline neuroticism with onset of various index disorders assessed one year later. The authors controlled for (i) baseline disorders and (ii) lifetime core symptoms of the index disorder. This study still found a moderate predictive effect of neuroticism on the incidence of mood disorders (OR = 2.18; $d = 0.47$) but not anxiety and substance use disorders (de Graaf et al., 2002). Krueger (1999) (n = 961) investigated the association between baseline neuroticism at age 18 and CMDs three years later. After adjusting for baseline symptoms, the effect of neuroticism at age 18 on later CMDs was still significant (anxiety disorders: $\beta = 0.18$; $d = 0.46$; depressive disorders: $\beta = 0.12$; $d = 0.34$; substance use disorders: $\beta = 0.09$; $d = 0.28$). After adjustment, Engelhard et al. found no prospective association between neuroticism and subsequent CMDs.

In sum, given the lack of full control, it remains unresolved whether neuroticism is a truly independent predictor of mental disorder. However, the evidence is suggestive that it is, at least to some extent, especially with regard to mood disorders. Furthermore, it is possible that the predictive power of neuroticism is underestimated in adjusted analyses to the extent that baseline psychiatric symptoms and earlier episodes are caused by neuroticism but are then adjusted.

4.4. Shorter versus longer intervals

Interestingly, Table 3 shows that the unadjusted effects over intervals longer than 3.6 years (mean $d = 0.53$) are not much smaller than those with intervals between 1 and 3.5 years ($d = 0.57$). To a lesser extent, this also holds true for the mean adjusted association between baseline neuroticism and later CMDs of $d = 0.22$ for long intervals versus $d = 0.39$ for short intervals. Only the adjusted association with later psychological distress showed a large difference between intervals, with $d = 0.14$ for long intervals and $d = 0.48$ for short intervals. These typically small differences between short and long follow-ups for CMDs indirectly support the vulnerability model, and are also consistent with the common cause model.

5. Operational confounding and the trait-state distinction

In addition to the issues related to adequate control for confounders, the interpretation of associations between neuroticism and CMD is also difficult because of the overlap between item content of neuroticism inventories and measures of CMDs (Duncan-Jones et al., 1990; Ormel, Rosmalen, et al., 2004). Many neuroticism items are similar to items of popular symptom measures in that they refer to the same affects, cognitions and behaviors (see for examples: Ormel, Riese, & Rosmalen, 2012).

However, there are two important differences, both of which relate to the distinction between trait and state. Symptom measures have specific time frames (typically 2–4 weeks) and are rated on severity, whereas neuroticism questionnaires typically ask how the respondent feels, thinks, and behaves in general, and use an agree/disagree rating scale. Furthermore, neuroticism measures assess global tendencies in emotions, cognitions, and behaviors that cut across situations, whereas symptom measures concern particular, often narrowly defined, symptoms. It is difficult to establish to what extent these two state-trait related differences make neuroticism measures fundamentally different from psychopathology measures. In as far as content overlap exists it provides support for the spectrum model.

6. Stability and change of neuroticism — different from psychopathology?

Rank-order stability data can shed light on the validity of the models. Rank-order stability reflects the stability of individuals' relative position within the group, also known as differential stability, and is typically established with test–retest correlations. Meta-analytic evidence shows increasing differential stability of personality with age until a peak in late adulthood, as well as decreasing stability with increasing time intervals between measurement occasions (Fraley & Roberts, 2005; Roberts & DelVecchio, 2000), with a meta-analytic correlation between time interval and differential stability of $r = -0.36$. Recent studies, not included in the meta-analysis, found similar or slightly higher differential stability estimates (Kandler et al., 2010; Lüdtke, Trautwein, & Husemann, 2009; Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008a; Terracciano, McCrae, Brant, & Costa, 2005). Two studies have assessed neuroticism at least four times over a period of about two decades. At the start of the studies the mean age was, respectively, 34 (SD 12; range 16–63) and 42 (SD and range not reported) (Ormel & Rijsdijk, 2000; Wray, Birley, Sullivan, Visscher, & Martin, 2007). Both studies reported a gradual decline in stability reaching about $r = 0.40$ over more than 20 years. Thus, empirical evidence has documented not only substantial differential stability of neuroticism during adulthood, but also sustained and cumulative change.

Based on the definition of states as compared to traits, we would expect CMDs and symptoms to be considerably less stable than neuroticism. However, longitudinal studies have found substantial differential stability of psychiatric symptoms (Duncan-Jones et al., 1990; Ormel & Schaufeli, 1991) and disorders as well (Conradi, de Jonge, & Ormel, 2008; Copeland, Shanahan, Costello, & Angold, 2009; Fergusson & Horwood, 2001; Krueger et al., 1998; Ormel, Oldehinkel, Brilman, & van den Brink, 1993; Shea & Yen, 2003; Vollebergh et al., 2001; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). These studies also show that half to one third of the patients experiencing a first brief episode of anxiety or depression do not develop a recurrence. However, if recurrence occurs, full and sustained recovery is less common and the long-term course is often unstable, with fluctuating severity levels

that may cross diagnostic thresholds repeatedly (Conradi et al., 2008; Monroe & Harkness, 2011; Ormel et al., 1993).

Ormel and Schaufeli reviewed 13 two-wave studies of anxiety and depressive symptoms with an average interval of 1 year in 1990 and found longitudinal correlations ranging from 0.30 to 0.70 (J. Ormel & Schaufeli, 1991). Later longitudinal studies yielded correlations for depressive and anxiety symptoms from 0.58 across a 4-month interval to 0.40 across 8 years (e.g. Duncan-Jones et al., 1990; Kendler & Gardner, 2011). Although never systematically investigated, the drop in symptom stability with increasing time intervals seems eventually to level off at an asymptotic level of 0.30–0.40 (Lovibond, 1998).

Longitudinal studies assessing both neuroticism and psychopathology at multiple points in time are uncommon. Table 4 shows the results of the larger population-based studies. The difference in stability is modest; stability is about a third higher for neuroticism than for CMD symptoms. In sum and with some caution, the differential stability of CMDs, especially at the level of symptoms, is somewhat lower than that of neuroticism but shows the same pattern: substantial but decreasing with increasing time intervals and eventually leveling off. Thus, there is more stability in CMD symptoms and more change in neuroticism than the concepts of state and trait would suggest.

7. Genetic and environmental determinants of neuroticism and CMDs

7.1. Twin studies

Neuroticism is the product of the interplay between genetic and environmental influences. Heritability estimates typically range from 40% to 60% (Eaves et al., 1999; Flint, 2004; Fullerton, 2006; Viken, Rose, Kaprio, & Koskenvuo, 1994). Similar or slightly lower heritability has been reported for CMDs (Boomsma, van Beijsterveldt, & Hudziak, 2005; Jardine, Martin, & Henderson, 1984; Kendler, Gardner, & Lichtenstein, 2008; McGuffin, Owen, & Gottesman, 2002; Shih, Belmonte, & Zandi, 2004). The genetic influences on neuroticism remain largely the same across adult life, whereas the environmental influences, largely nonshared, are relatively occasion-specific, suggesting chance and age effects (Kandler et al., 2010; McGue, Bacon, & Lykken, 1993; Viken et al., 1994; Wray et al., 2007). The temporal stability of environmental influences tends to increase with age (Kandler et al., 2010; McGue et al., 1993; Viken et al., 1994; Wray et al., 2007). For CMDs such as anxiety and depression, a similar stability pattern of genetic and environmental influences has been reported (Kendler, Aggen, et al., 2011; Kupper, Boomsma, de Geus, Denollet, & Willemsen, 2011).

Most importantly here, the genetic sources of neuroticism and CMDs (especially the internalizing disorders) overlap as indicated by the considerable genetic correlation between neuroticism and CMDs (Carey & DiLalla, 1994; Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler & Myers, 2010; Kendler et al., 1993; Middeldorp, Cath, van Dyck, & Boomsma, 2005). For instance, Hettema and colleagues analyzed data on neuroticism and internalizing disorders from over 9000 male and female twins, and found that the genetic correlations between neuroticism and these disorders were high, ranging from 0.58 to 0.82; whereas the environmental correlations were much lower and ranged from 0.05 to 0.27. Thus, phenotypic neuroticism-internalizing disorder associations are largely due to shared genetic factors.

The hunt for specific genes related to neuroticism and CMDs has turned out to be difficult and hardly successful so far. Initial optimism (Ebstein, 2006; Fullerton, 2006; Wray et al., 2008) has been tempered by meta-analyses (McCrae, Scally, Terracciano, Abecasis, & Costa, 2010; Shifman et al., 2008) that did not find robust support for any of the candidate genes proposed. Thus, the specific genes that neuroticism and CMDs have in common remain elusive, but it is well established that these phenotypes share substantial genetic variance.

These findings strongly support the common cause and spectrum models for internalizing disorders. However, the authors also identified a neuroticism-independent genetic factor that sizably increased risk of major depression, generalized anxiety disorder, and panic disorder. This is inconsistent with the common cause and spectrum models. Although much less studied, some evidence of weak to moderate genetic correlation between neuroticism and non-internalizing CMDs such as the substance use disorders has been reported as well (Carey & DiLalla, 1994; Kendler, Karkowski, Corey, Prescott, & Neale, 1999; Kendler, Prescott, Myers, & Neale, 2003; Littlefield et al., 2011; Sher & Trull, 1994).

Table 4
Test–retest correlations for neuroticism and symptom measures.

Year	First author	Sample	Women %	Age in years M (SD)	Test–retest interval in years		Psychopathology measure	Instrument	Test–retest correlation
2012	Jeronimus	2981	67	18–65 M = 42 (13.1)	2		Neuroticism	NEO-FFI	.78
						Sx	Depression	IDS-SR30	.72
						Sx	Anxiety	BAI	.69
2011	Prenoveau	627	69	M = 17 (0.4)	1,2,3		Neuroticism[a]	Big 5-N/IPIP-N/BIS	.86, .83, .75
					1,2,3	Sx	Depression[a]	MASQ/IDD	.62, .46, .46
					1,2,3	Sx	Social anxiety[a]	SCID-CSR/SPS-SC	.73, .70, .59
					1,2,3	Sx	Specific phobia[a]	SCID-CRS/FSS-II	.76, .74, .64
2004	Neeleman	3625	68	18–65 M = 42 (12.2)	3		Neuroticism	EPI	.65
						Sx	Psychiatric morbidity	CIDI	.52
						Sx	Somatic morbidity	Checklist[b]	.64
2000	NEMESIS	4839	55	18–65 M = 41	1,2,3	Sx	Neuroticism	EPI MOS-PSY	.73 .70 .68
							Psychological distress		.57 .53 .51
2001	Wetherell	1391	57	29–95 M = 61 (13.3)	3,6		Trait anxiety	STPI	.58, .55
					3,6	Sx	Depression	CES-D	.55, .52
1989	Fergusson	1052	100	20–40[c]	1		Neuroticism	EPI	.60
						Sx	Depression	LPDQ	.49
1991	Ormel	296	44	16–63 M = 34 (11.8)	1,2,11		Neuroticism	ABV	.74, .70, .51
					1,2,11	Sx	Depression	BNA	.60, .52, .40

ABV = Amsterdamse Biografische Vragenlijst; BAI = Beck Anxiety Inventory; BIG 5-N = Big-Five Mini-Markers Neuroticism scale; BIS = Behavioral Inhibition System Scale; BNA = Bradburn negative affect; FSS-II = Fear Survey Schedule II; IDD = Inventory to Diagnose Depression; IPIP-N = International Personality Item Pool, 2001; LPDQ = Levine Pilowsky Depression Questionnaire; MASQ = Mood and Anxiety Symptom Questionnaire; SCID CSR = Structural clinical interview for DSM-IV social phobia; SPS-SC = Self-Consciousness subscale of the Social Phobia Scale; STPI = State-Trait Personality Inventory; Sx = symptoms.

[a] Latent constructs.

[b] Checklist concerning experience with 22 somatic conditions during the two years preceding T_2.

[c] 13.2% ≤ 27, 33.8% aged 28–32, 26.6% 33–37 and 16.3% ≥ 35.

7.2. Environmental influences

In contrast to genes, several specific environmental factors were found to be shared by neuroticism and CMDs. Childhood and adolescent adversities have been linked to neuroticism and many forms of psychopathology in adulthood (Gilbert et al., 2009; Kessler, Davis, & Kendler, 1997; Rosenman & Rodgers, 2006; Roy, 2002). These adversities include emotional neglect and sexual abuse (Allen & Lauterbach, 2007; Edwards, Holden, Felitti, & Anda, 2003; Green et al., 2010; Kendler, Davis, & Kessler, 1997; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Roy, 2002), poor parental care (Reti et al., 2002), highly intrusive parenting (Reti et al., 2002), childhood trauma (Roy, 2002), and being bullied (Roberts, Wood, & Smith, 2005; Rutter, 2006; van Os & Jones, 1999). Most of the human evidence rests upon retrospective reports of childhood adversity with all their limitations for reliability and validity (Hardt & Rutter, 2004). A few prospective studies have related early adversity to later neuroticism and CMDs (Fergusson & Horwood, 2001; Gilbert et al., 2009; Roy, 2002; Scott, Smith, & Ellis, 2010; van Os & Jones, 1999). Collectively, these studies suggest that without adequate social support, uncontrollable, high-intensity childhood stressors are risk factors for both CMDs and elevated neuroticism in adulthood.

The substantial differential stability of neuroticism and the fluctuating-chronic nature of recurrent CMDs suggest that experiences with the capacity to cause sustained change in neuroticism and mental health are rather rare or have only small effects. A potential source of persistent change is exposure to powerful stressors, in particular during adolescence and young adulthood, which has been indicated to contribute to neuroticism and CMDs later in life (Fergusson & Horwood, 2001; van Os & Jones, 1999). Other possible change agents are success and failure in the major social roles of marriage and work, in particular when they accumulate over time (Caspi et al., 2005; Roberts, Wood, et al., 2005). The formation of a romantic relationship, marriage, marital satisfaction, and satisfying and engaging employment are associated with decreases in neuroticism (Lucas, Clark, Georgelis, & Diener, 2004; Lüdtke, Roberts, Trautwein, & Nagy, 2011; Lüdtke et al., 2009) and CMD risk (Leenstra, Ormel, & Giel, 1995; Lucas et al., 2004; Ormel & Wohlfarth, 1991). In contrast, conflicts, poor relationship quality, and chronic or repeated unemployment can lead to increases in neuroticism (Costa, Herbst, McCrae, & Siegler, 2000; Lucas et al., 2004; Lüdtke et al., 2009; Lüdtke et al., 2011) and CMD risk (Brown & Harris, 1989; Kendler, Gardner, & Prescott, 2002; Kendler, Gardner, & Prescott, 2006; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Ormel & Wohlfarth, 1991; Tiet et al., 2001).

Collectively, studies on the role of childhood and adolescent adversities suggest that poor parenting and childhood trauma in early life as well as uncontrollable stress in adolescence play a role in shaping both adult neuroticism and CMDs. Subsequent major life events and successes or failures in social roles continue to shape both domains throughout the lifespan. These shared determinants likely contribute to the prospective neuroticism–CMD links and as such provide support for the common cause and hence the spectrum model as well because the spectrum model (neuroticism and psychopathology reflect the same processes) assumes fully shared determinants as well.

7.3. Transactions between neuroticism and life stress

Multiple longitudinal studies have found that the lifestyles of high-neuroticism individuals increase the likelihood of stressful experiences, and that these stressors in turn can trigger CMDs, e.g. (Hankin, Stone, & Wright, 2010; Kercher, Rapee, & Schniering, 2009; Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008b; Ormel & Wohlfarth, 1991). This evidence of stress-generation suggests that neuroticism may have causal effect on CMDs via life stress. Furthermore, high-neuroticism individuals have been found to be at greater risk of CMDs following exposure to stressful life events (Bolger & Schilling, 1991; Kendler & Prescott, 2006; Ormel & Wohlfarth, 1991; Ormel et al., 2001; van Os et al., 2001), but this moderating effect has not been found in all studies (Engelhard, van, & Lommen, 2009). Nevertheless, significant evidence has accumulated in support of this diathesis-stress effect; suggesting that both neuroticism and life stress contribute to development of CMDs and that a combination of the two risk factors is especially potent (Kendler & Prescott, 2006; Ormel et al., 2001). This supports the vulnerability model.

8. Treatment response

There is some evidence that the treatment of depression also reduces neuroticism (Zinbarg, Uliaszek, & Adler, 2008) and that this effect is not entirely due to confounding by the change in depressive state (Tang et al., 2009). Indeed, Quilty and colleagues found that decrease in neuroticism mediates treatment effect on depression (Quilty, Meusel, & Bagby, 2008). More evidence has accumulated that psychiatric treatment has better outcomes in individuals with relatively low neuroticism but the evidence is largely limited to depression (Kennedy, Farvolden, Cohen, Bagby, & Costa, 2005; Klein et al., 2011; Mulder, 2002; Tang et al., 2009). Other explanations need to be ruled out, however, such as that traits predict worse response because they indicate a more severe form of mental disorder or that they interfere with treatment compliance and the therapeutic relationship, thus reducing the efficacy of the intervention.

9. Implications of evidence for validity of neuroticism–CMD models

Summary of evidence for and against the models is given in Table 5. Much evidence lacks decisive implications for a particular model, presented as +/− in Table 5. At first none of the models seem a clear winner, in that it is capable to account for (virtually) all evidence. Neither does the evidence completely rule out the common cause, spectrum or scar model, although the latter is not very likely because the few studies who found scar effects on neuroticism may have been dealing with decaying state effects (Ormel, Oldehinkel & Vollebergh, 2004). The state model cannot explain the *prospective* association between neuroticism and the subsequent onset of a first-ever CMD. This does not imply that the state model itself is invalid, in contrary, it is firmly established that neuroticism scores are substantially increased during episodes of most CMDs compared to pre- and post-episode times (Costa, Bagby, Herbst, & McCrae, 2005; Kendler et al., 1993; Ormel, Oldehinkel and Vollebergh, 2004; Rohde et al., 1994). In addition, psychometric studies indicate that neuroticism scores include some state variance that is independent of developmental changes in the traits but related to current affective state (Chmielewski & Watson, 2009; Watson, 2004).

The spectrum model cannot explain much prospective association between neuroticism and internalizing disorders, but some aspects of it are likely true and do account for some prospective association. These aspects include the overlap in item content, the synchrony of change, and the moderate similarity in rank-order stability. Particularly the existence of risk factors unique to neuroticism or internalizing disorders argues strongly against the spectrum model as the dominant explanatory model. The fact that the prospective relationship of neuroticism with CMDs is not specific to the internalizing disorders argues also against a full explanation by the spectrum model. After all, neuroticism's item content overlap concerns the internalizing disorders; the diagnostic criteria of substance use disorders do not include neuroticism.

The common cause model garnered substantial support including shared determinants (especially genetic) and synchrony of change. It is also consistent with much evidence but not in an unequivocal manner (the +/− items in Table 5). Thus, most prospective association could be due to common causes. However, a dominant common cause model has difficulty accounting for the unique determinants of neuroticism and the internalizing disorders. It has also difficulty to account for the

Table 5
Evaluation of models in light of the evidence on neuroticism (N) and internalizing disorders (INT).

The evidence	State	Scar	Vulnerability	Common cause	Spectrum
Cross-sectional association neuroticism–CMD	++	++	+/−	++	++
Prospective association neuroticism–CMD	–	+/−	++	+/−	–
N enhances life stress effect on psychopathology	–	–	++	+/−	–
Substantial item content overlap	–	–	-	–	++
Partly shared determinants	–	–	-	++	+/−
Partly unique determinants	–	–	++	–	–
Synchrony of change	+/−	+/−	-	+	+/−
N is more stable than INT	+/−	-	+ (1)	+ (2)	-
Post-episode N probably not higher than pre-episode N	+	–	+/−	+/−	+/−
Treatment effect mediated by N	-	+/−	++	+/−	+/−

Note. + (++), (strongly) consistent with model; – (–), (strongly) inconsistent with model.
+/−, lacks a clear implication. 1, if difference is marked. 2, if difference is small.

prospective association, especially across long intervals of multiple years, and the life stress moderating effect of neuroticism.

In contrast, the latter two findings are consistent with the vulnerability model, especially if the prospective association would remain substantial when fully adjusted for psychiatric confounders. The evidence suggests that it will to some extent. Also consistent with the vulnerability model is the mediating and moderating role of life stress and the partly unique determinants. It is in particular the item content overlap, shared determinants, and the synchrony of change which argue strongly against the vulnerability model as the dominant explanatory model for the association between neuroticism and internalizing disorders.

It is important to take into account the specific CMD. Regarding anxiety disorders, the evidence favors a major role for the common cause model, with similar evidence for the spectrum and vulnerability model. Regarding depressive disorders, the common cause model again has the strongest support but is followed by the vulnerability model; data for the spectrum model is the weakest. With regard to substance use disorders, which are substantially less strongly predicted by neuroticism compared to anxiety and depressive disorders, vulnerability and common cause model receive the strongest support. Substance use disorders can develop as maladaptive forms of coping with high levels of negative affect characteristic for high neuroticism (Khantzian, 1997; Swendsen et al., 2000), which is consistent with the vulnerability model. Furthermore, substance use disorders somewhat share genetic and environmental determinants with internalizing disorders (Kendler, Aggen, et al., 2011; Kendler, Prescott, et al., 2003) and, as documented earlier, with neuroticism. These determinants include early adversity, life stress, and non-adaptive coping strategies. This supports the common cause model. None or little support was found for the scar and spectrum models. Note that the evidence is limited to substance use disorders; the evidence on other externalizing disorders is virtually lacking.

In conclusion, no model by itself is able to fully account for the evidence. The common cause and vulnerability models, and to a lesser extent the spectrum model, each receive significant empirical support, but the degree of support depends on the CMD of interest. The association of neuroticism with substance use disorders is best interpreted by a combination of the vulnerability and common cause models. The state and scar models very likely do not account for any prospective association. Fig. 1 depicts a tentative "integrated" model for internalizing and substance use disorders.

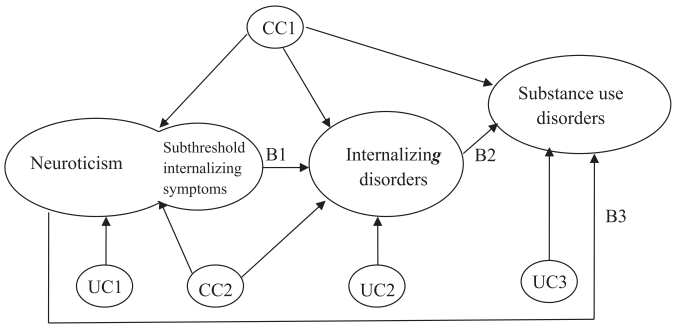
10. Schematic model of the relationship between neuroticism and CMDs

10.1. Next steps

These conclusions are necessarily tentative because the existing literature has several limitations. First, few prospective studies controlled for all relevant baseline symptoms and psychiatric history, thus, unique predictive power of neuroticism has not yet been established. Second, while we found substantial evidence directly supporting the common cause and the spectrum models, there are still relatively few data on mechanisms that may convey risk from neuroticism to CMDs, and the pathways are far from established. Behavior genetics has elucidated the basic architecture of neuroticism–CMD link, the specific genetic mechanisms involved are not yet known, and understanding of environmental pathways is fragmentary as well, although inspiring evidence is emerging (Depue, 2009; Hankin et al., 2010; Lahey, 2009; Ormel, Bastiaansen, et al., 2012; Suls & Martin, 2005). For instance, neuroticism has been linked to negative bias in attention, interpretation, and recall of information; stressful event generation; relatively ineffective coping; and probably also with increased reactivity and affect variability (Ormel, Bastiaansen, et al., 2012; Suls & Martin, 2005). These characteristics may drive the proximal processes that trigger or maintain CMDs. Third, there are too few prospective behavioral genetic studies to know whether neuroticism contributes to onset of CMDs beyond shared genetic and environmental determinants of psychopathology. Fifth, an overarching concern is the scarcity of comprehensive studies. The majority of investigations have focused on depression or substance use disorders; for instance, specific anxiety disorders, antisocial behavior, and psychotic disorders received little attention.

To make further progress, it is crucial to test not only mediation of treatment effects in CMD patients but also whether preventive interventions that specifically target neuroticism in *non-affected* high neuroticism samples reduce future CMD risk. Evidence that change in neuroticism does predict change in CMD risk would be most compelling in differentiating between the vulnerability and common cause models. Emerging evidence suggests that both pharmacological and psychosocial interventions may succeed in reducing neuroticism (Tang et al., 2009; Zinbarg et al., 2008), but hardly a single study has been designed to critically test whether this effect is independent from improvement in mental health status. Other steps are important as well. One is to intensify the efforts to elucidate the psychological and biological basis of neuroticism, [see for a review (Ormel, Bastiaansen, et al., 2012)]. Future studies should also seek to move beyond self-report and use other measures of neuroticism, such as informant ratings (Kotov et al., 2010).

Last but not least, there is a need to deconstruct neuroticism. The majority of personality–psychopathology studies use the broad personality trait measures. More research at the level of neuroticism's facets will likely yield important data on the neuroticism–CMDs relationship, as the facets may contain additional variance relevant to the elucidation of the relationship (Paunonen & Ashton, 2001). Studying neuroticism's facets may reveal differential and even antagonistic processes (Chioqueta & Stiles, 2005; Oldehinkel, Hartman, de Winter, Veenstra, & Ormel, 2004; Ormel et al., 2005; Schmitz, Hennig, Kuepper, & Reuter, 2007). For instance the neuroticism facet of frustration acts as a general risk factor for both internalizing and externalizing symptoms in adolescents, while the neuroticism facets of fearfulness and shyness have rather specific effects (Chioqueta & Stiles, 2005; Oldehinkel et al., 2004; Ormel et al., 2005; Schmitz et al., 2007). Shyness increases risk of internalizing symptoms but protects against externalizing problem



Legend. CC1= common causes of neuroticism, internalizing symptoms and disorders and substance use disorders; CC2= common causes of neuroticism and internalizing symptoms and disorders; UC1-3= causes unique to neuroticism, internalizing disorders and substance use disorders, respectively; B1-3= causal effects.

Fig. 1. Tentative model of the relationship between neuroticism and CMDs disorders. Legend. CC1 = common causes of neuroticism, internalizing symptoms and disorders and substance use disorders; CC2 = common causes of neuroticism and internalizing symptoms and disorders; UC1-3 = causes unique to neuroticism, internalizing disorders and substance use disorders, respectively; B1-3 = causal effects.

behavior. This differentiation is theoretically meaningful and consistent with research in children and adults (Caspi et al., 2005; Rothbart, Ahadi, & Evans, 2000; Shiner & Caspi, 2003; Widiger et al., 1999).

Another argument supporting deconstruction of neuroticism flows from the emerging network approach to personality (Cramer et al., 2012). The network approach posits that personality traits emerge from the interactions between affective, cognitive and behavioral components (the neuroticism items, or small sets of strongly associated items). According to the network approach, these components are not associated because they are driven by a latent entity of neuroticism but because they influence one another over time (Cramer et al., 2012). The authors show that deconstruction of neuroticism in terms of interdependent components offers new perspectives on a variety of issues including the difficulties finding neuroticism genes.

10.2. Utility of neuroticism in psychiatric research

Does neuroticism have any utility in psychiatric research before its basis and determinants are understood? Given its predictive power, the neuroticism score can be used as a dimensional marker of unspecified general risk, both genetic and non-genetic, for developing psychopathology. These risks are not behaviorally silent but express themselves in subtle impairments in multiple domains of functioning and associated personal distress, which neuroticism items pick up (Ormel, Oldehinkel, Nolen, et al., 2004). Furthermore, because neuroticism measures are easy to administer, they represent a simple, efficient, reliable, and valid dimensional measure of the effectiveness of treatment and prevention programs. While this value is unproblematic, it is not certain whether neuroticism is an epiphenomenon of underlying etiologic processes (i.e., common cause model) or directly causal, in the sense that interventions targeting neuroticism specifically can modify CMD risk via changes in the trait (i.e., vulnerability model).

10.3. Concluding comments

Neuroticism has been labeled the single most important risk factor in behavioral public health (Lahey, 2009), and the economic costs of high neuroticism are estimated to exceed those of CMDs combined (Cuijpers et al., 2010). The literature we reviewed indicates that (1) neuroticism predicts onset of CMDs even after controlling for most (*but not all*) psychiatric confounders; (2) items used to assess neuroticism partially overlap with CMD symptoms, especially for internalizing disorders; (3) neuroticism and CMDs share substantial but not all genetic and environmental determinants; (4) neuroticism has higher temporal stability than CMD symptoms, although the difference is smaller than commonly thought; (5) neuroticism probably moderates the impact of life stress on CMD; and (6) reductions in neuroticism may partially mediate the effect of treatment on CMDs.

The association between neuroticism and CMDs has inspired multiple explanatory models, known as the vulnerability, spectrum, common cause, state, and scar models. None of these models is a clear, outspoken winner, in that it is capable to account for (virtually) all of the prospective neuroticism–CMD association. Neither does the evidence completely rule out any of these models, with the exception of the state and probably the scar model as well. Especially the common cause and vulnerability model, and to a lesser extent the spectrum model, account each for part of the prospective neuroticism–CMD association. Furthermore, it is important to take into account the specific CMD. Regarding the anxiety disorders; the evidence favors a major role for the common cause model, followed by the spectrum and vulnerability models. Regarding the depressive disorders, the vulnerability model becomes second best after the common cause model but before the spectrum model. Regarding the substance use disorders, the vulnerability model may account for most prospective association, followed by the common cause model.

To test these preliminary conclusions, intervention studies offer the best options. Studies that test whether treatment effects in CMD patients go hand in hand with reductions in neuroticism and shared determinants will evaluate the common cause model. Studies that examine to what extent preventive interventions targeting neuroticism in non-affected high neuroticism individuals do reduce future CMD risk are relevant for the vulnerability model. Longitudinal studies that test to what extent the prospective association drops with comprehensive control for psychiatric history and baseline psychiatric symptoms will inform on the validity of the spectrum model. Further progress is probably also facilitated by deconstructing neuroticism in facets (or components), identified as small sets of items that are strongly associated because they influence each other or share a common cause such as a neurobiological or psychological system (Ormel, Bastiaansen, et al., 2012; Ormel, Riese, et al., 2012).

Are our conclusions regarding the neuroticism–CMDs relationship relevant for understanding the relationship of other personality traits with psychopathology? As mentioned earlier, low conscientiousness, (dis)inhibition, and extraversion, have all been linked to CMDs as well, though less strongly. Although only empirical data can answer this question, it seems likely that the operational overlap between these traits and CMDs is significantly smaller than it is for neuroticism. If prospective studies uphold the cross-sectional association,

the smaller operational overlap would tend to invalidate the spectrum and state models, providing further support for the vulnerability and common cause models.

To date, the utility of neuroticism is mainly that it is a highly efficient marker of risk, both genetic and non-genetic, for developing psychopathology, but without specifying the etiological processes involved (Clark & Watson, 1999; Lahey, 2009). Neuroticism's prospective association with CMDs in itself does not elucidate the mechanisms underlying their association. Thus, for the time being, neuroticism is best conceptualized as a variable in need of explanation. The value of neuroticism as an efficient marker should not be underestimated. Given the etiological overlap between neuroticism and CMDs, research that succeeds in elucidating the (psycho) biological basis and determinants of neuroticism will inform on the etiology of not only neuroticism but CMDs as well. Such research will facilitate treatment and prevention programs that target the core of common mental disorders and not just their specific manifestations.

Declaration of interest

Authors report no conflict of interest.

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