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Journal of Affective Disorders 295 (2021) 1347–1359

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review Article

Psychological risk factors and the course of depression and anxiety disorders: A review of 15 years NESDA research

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ARTICLE INFO

Keywords:
Depression
Anxiety
Psychological vulnerability
Psychological risk factors
Review
Affective disorders

ABSTRACT

Background: The Netherlands Study of Depression and Anxiety (NESDA; $N_{baseline}$=2981) is an ongoing longitudinal, multi-site, naturalistic, cohort study examining the etiology, course, and consequences of depression and anxiety. In this article we synthesize and evaluate fifteen years of NESDA research on prominent psychological risk factors for the onset, persistence, recurrence, and comorbidity of affective disorders.

Methods: A narrative review of 62 NESDA articles examining the specificity and predictive value of neuroticism, behavioral inhibition, repetitive negative thinking, experiential avoidance, cognitive reactivity, locus of control, (implicit) self-esteem, (implicit) disorder-specific self-associations, and attentional bias for the course of affective disorders.

Results: All self-reported risk factors showed cross-sectional relationships with singular and comorbid affective disorders, and prospective relationships with the development and chronicity of depression and anxiety disorders. High neuroticism, low self-esteem, and negative repetitive thinking showed most prominent transdiagnostic relationships, whereas cognitive reactivity showed most pronounced depression-specific associations. Implicit self-esteem showed predictive validity for the persistence and recurrence of anxiety and depression over and above self-reported risk factors. Automatic approach-avoidance behavior and attentional bias for negative, positive, or threat words showed no relationship with affective disorders.

Conclusion: NESDA identified both (a) transdiagnostic factors (e.g., neuroticism, low implicit self-esteem, repetitive negative thinking) that may help explain the comorbidity between affective disorders and overlap in symptoms, and (b) indications for disorder-specific risk factors (e.g., cognitive responsivity) which support the relevance of distinct disorder categories and disorder-specific mechanisms. Thus, the results point to the relevance of both transdiagnostic and disorder-specific targets for therapeutic interventions.

1. Introduction

Depression and anxiety disorders represent major problems for public health (Ormel et al., 2008). The disability and health care costs of depression and anxiety disorders are especially high due to their chronic (intermittent) course (Mathers and Loncar, 2006). Despite several effective treatments, recurrence is common in both depression and anxiety disorders (Bruce et al., 2005; Hardeveld et al., 2013). Taking also diagnostically unstable recurrence into account, reported recurrence rates are as high as 66.3% (Scholten et al., 2016). This points to the importance of improving our understanding of factors involved in the origin, chronicity, and recurrence of affective disorders. This was the prime reason for the Dutch Organization for Health Sciences to grant funding in 2004 for a large scale, long-term longitudinal research program focusing on depressive and anxiety disorders: The Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl). The design of NESDA provided an excellent infrastructure to examine psychological risk factors involved in the (chronic) course of affective disorders. In this

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https://doi.org/10.1016/j.jad.2021.08.086
Received 31 May 2021; Received in revised form 24 August 2021; Accepted 26 August 2021
Available online 1 September 2021

Table 1
Sample characteristics at the various waves of the Netherlands Study of Depression and Anxiety (NESDA).

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
Average follow-up duration since baseline	Baseline	1 year	2 years	4 years	6 years	9 years
Sample size	2981	2445	2596	2402	2256	2069
Response rate	na	82.0%	87.1%	80.8%	75.7%	69.4%
Persons with current* anxiety and/or depressive disorders	57.1%	na	37.4%	31.9%	28.5%	27.5%
Persons with remitted** anxiety and/or depressive disorders	21.1%	na	41.7%	48.1%	51.7%	53.4%
Persons without any lifetime anxiety and/or depressive disorders	21.9%	na	20.9%	20.0%	19.8%	19.1%

Note. * current is based on 6-month recency
** remitted is based on lifetime, but not current, diagnosis; na = not available.

review we synthesize fifteen years of NESDA research on the relevance of prominent candidate psychological risk factors in the development and course of depression and anxiety disorders, condensed in more than sixty articles, and critically reflect on how these findings might inform treatment of affective disorders.

At the start of the study, NESDA included persons diagnosed with a current depression and/or anxiety disorder, a history of depression and/or anxiety disorder, and individuals without a current or past disorder (Penninx et al., 2008). Participants were recruited from 2004 to 2016 in different settings (general population, primary care and mental health care organizations), in multiple waves (baseline, 1, 2, 4, 6 and 9 year follow-up). At baseline 57% of participants were diagnosed with a current affective disorder (Table 1). NESDA's ultimate aim was to provide starting points for improving treatment options. Therefore, the emphasis of the psychological measures that were included in NESDA was on malleable risk factors.

Due to its large sample size and longitudinal design, NESDA provided an excellent opportunity to complement available evidence on psychological risk factors in multiple important ways. First, earlier cross-sectional findings could be replicated in a well-powered study that allowed for comparison of well-defined clinical groups, including remitted individuals, and those with comorbid disorders. Second, NESDA allowed researchers to test the disorder-specificity of particular risk factors. At the start of NESDA, most research examining psychological factors in affective disorders was restricted to particular disorder (e.g., cognitive reactivity in depression), precluding the opportunity to test whether this particular factor might more generally contribute to affective disorders (i.e. having a 'transdiagnostic' association with both anxiety and depression). Third, prospective relationships of particular psychological measures with both remittance and chronicity, as well as the development of comorbidity could reliably be examined. Fourth, the inclusion of multiple psychological measures during the same assessment wave allowed to examine to what extent the relationships between particular risk factors and the course of affective disorders represented unique or (partly) overlapping relationships. Fifth, NESDA not only relied on self-report measures but also included implicit performance-based measures of constructs that are central to cognitive models of emotional disorders but are not accessible to introspection such as attentional bias (Bar-Haim et al., 2007; McCabe et al., 2000), negative automatic self-associations (Beevers et al., 2015) and automatic approach/avoidance behavior (Rinck and Becker, 2007). Finally, the inclusion of individuals without a history of affective disorders provided a helpful reference group to examine the relevance of the included psychological measures as risk factors for the first onset of anxiety and/or depression disorders in those who developed a first episode after inclusion in the study (Glashouwer et al., 2011; Kruijt et al., 2013).

In line with dimensional models of psychopathology, NESDA included anxiety and depression symptom severity measures next to categorical measures based on a clinical interview. This further facilitated empirical scrutiny of general versus disorder specific involvement of the psychological risk factors in affective disorders. To guarantee the study's feasibility and to promote participants' long-term commitment for repeated assessments over a (very) long time span, only a very limited number of measurement instruments could be part of the study. Initial selection of measures was heavily inspired by the rapidly accumulating evidence in the late 1990s and early 2000s for the importance of dysfunctional cognitive processes in the development of affective disorders (Mathews and MacLeod, 2005), which still is highly topical (Teachman et al., 2019).

We selected measures of constructs that already showed promise as a candidate risk factor in earlier research in the context of anxiety (e.g. anxiety sensitivity; Taylor, 1999), and depression (e.g., cognitive reactivity; Segal et al., 1999), and measures of mechanisms that showed promise in both anxiety and depression disorders (e.g., repetitive negative thinking; Papageorgiou and Wells, 2008). Next to these relatively specific psychological constructs, also more generic trait characteristics/personality dimensions with an established link to psychopathology were measured (e.g., neuroticism; Ormel et al., 2004)

Each of these psychological risk factors in NESDA shall be introduced below and we review their key outcomes across all articles listed under 'psychological vulnerabilities' on the NESDA website (https://www.nesda.nl/publication-category/psychological-vulnerabilities/). Each section sets out to answer the following research question: "what are the cross-sectional and prospective relationships of psychological risk factors studied within NESDA with affective disorders and their comorbidities?" This review concludes with an integration of the overall pattern of findings and a reflection on the relevance of differentiating between general and disorder-specific risk factors, and how this connects to our understanding and treatment of affective disorders.

2. Personality

2.1. Basic personality dimensions

Personality captures relatively stable patterns of feelings, thoughts, needs, wants, and behavior over time and across context (John et al., 2008). Undesirable extremes of normal personality variation have historically been understood as psychopathology, a notion that regains influence within psychiatry (Bucher et al., 2019; Kotov et al., 2017). Personality differences comprise the broadest conceptual level of psychological risk in NESDA and were operationalized using the Big Five personality factors of neuroticism, extraversion, conscientiousness, agreeableness, and openness to new experiences (Costa and Mccrae, 1995).

Neuroticism and extraversion were the most studied risk factors of emotional disorders in NESDA, and were also often included in articles that focused on other (psychological) risk factors. The Big Five was assessed at baseline and at two- and four-year follow-up, showing a mean-level decrease in neuroticism (from M = 36.3 [SD= 9.4] to 32.7 [8.5]), and an increase in extraversion (M = 36.9 [7.4] to 38.1 [7.4]; see Struijs et al., 2020). As extraversion levels typically decrease over adulthood this suggests that the NESDA trajectory is likely to reflect recovery from baseline affective problems. Across the NESDA studies highly specific subgroups of participants were selected, and average neuroticism scores therefore differed substantially across papers (from M = 15.40 [7.40] to 46.00 [5.70]), just as for extraversion (from M =

29.90 [6.20] to 42.60 [6.20]). Studies using conscientiousness, agreeableness, and openness showed comparable mean-level differences.

Neuroticism captures a broad vulnerability index from characteristic levels of negative affect and self-consciousness, avoidance, vigilance, worry, rumination, to increased sensitivity to threat, punishment, and uncertainty (Ormel et al., 2013). Neuroticism also underlies the concept of a neurobiological Behavioral Inhibition System and avoidance motivation (BIS; Larsen et al., 2020). High extraversion taps into the tendency to experience frequent intense positive affect and to be sociable, assertive, energetic, risk-taking, and excitement seeking, versus being more reserved and solitary. Dispositional optimism, a positive attitude to life and generalized positive expectations towards the future (Carver et al., 2010), and the Behavioral Approach System (BAS) both refer to motivational systems that are also measured by extraversion (Larsen et al., 2020). High conscientiousness taps into the tendency to be self-disciplined (achievement oriented), persistent, reliable, ordered, and dutiful (norms/rules), and captures the self-regulation that plays a protective role during the development of emotional disorders and during recovery. High agreeableness captures the tendency to be kind, cooperative, trustworthy, trusting, generous and empathic. High openness to new experiences taps into the tendency to be perceptive, creative, reflective, flexible, curious, and to appreciate fantasy, aesthetics, and novelty.

2.1.1. Cross-sectional associations

The basic personality dimensions showed moderate to strong intercorrelations (r = .30 to .70), and substantial associations with anxiety and depression symptom severity and disorders (effect size r = .55 to .85, see Kok et al., 2017; Mesbah et al., 2019; Noteboom et al., 2016; Spinhoven et al., 2013, 2014). Compared to individuals without a history of affective problems, individuals diagnosed with anxiety (i.e., GAD, agoraphobia, and panic disorder), and depression (i.e., MDD, dysthymia) disorder, were characterized by higher neuroticism and lower extraversion and conscientiousness scores (Cohen's d > 0.80) and lower agreeableness (d = ~0.50). The personality differences between the diagnostic groups were much smaller in comparison (ds < 0.50). In multivariate models, disorder groups were marked by high neuroticism levels (Noteboom et al., 2016) and low extraversion as reflected in low positive affect and low sociability (Spinhoven et al., 2014).

Neuroticism showed substantial correlations with many of the more specific psychological risk factors, such external locus of control (LoC), hopelessness, rumination, worry, experiential avoidance, and fearful avoidance (r = .65 to .80); and all these specific risk factors also showed substantial correlations with cognitive reactivity (r > .50, Kruijt et al., 2013) and low extraversion (r ≤ -.45, see Boschloo et al., 2010; Drost et al., 2014; Glashouwer et al., 2011, 2012; Hovenkamp-Hermelink et al., 2019; Kok et al., 2017; Spinhoven, Elzinga, et al., 2015; Spinhoven, Drost, et al., 2016; Struijs, Lamers, Spinhoven, et al., 2018; Struijs et al., 2020). These concepts are thus all closely related.

Happiness and emotional well-being levels were highest in participants without a history of affective problems, followed by participants who recovered from an anxiety and/or depressive disorder, and lowest in participants with current affective problems (Spinhoven, Elzinga, et al., 2015). Extraversion and to a lesser extent neuroticism consistently forecasted future happiness and emotional well-being, also when the model was statistically controlling for concurrent measurements of affective disorders and symptoms, which may (temporarily) influence personality scores. Most participants with a current anxiety or depression disorder were reasonably happy, but among those with comorbid problems, almost half felt unhappy to a certain extent. Dispositional optimism was associated with a lower risk of current anxiety, depression, and their comorbidity, and fewer current and past mood disorders (Broekhof et al., 2015).

2.1.2. Longitudinal relationships

Individuals who did not improve in their anxiety and depression over two to six years follow up as indexed by clinical interview (CIDI) and symptom measures (BAI/IDS-SR) typically reported higher baseline neuroticism and lower conscientiousness and extraversion (Karsten et al., 2012; Spinhoven et al., 2012). The personality scores showed correlated changes with the occurrence, recovery, or persistence of affective disorders over time (Karsten et al., 2012; Spinhoven et al., 2013), indicative of their intimate co-development. Especially neuroticism predicted unfavorable course trajectories of anxiety and depression symptoms and disorders over up to nine years follow-up (OR = 1.24 to 1.66). Part of the prospective effect of neuroticism on anxiety and depression was mediated by more stressful life events (Jeronimus et al., 2013). Also, low extraversion and poor sociability (OR = 0.61-0.83) were risk factors for such unfavorable trajectories (see Hovenkamp-Hermelink et al., 2019; Hovens et al., 2016; Spinhoven et al., 2011, 2013; Struijs et al., 2013; Struijs, Lamers, Spinhoven, et al., 2018; Struijs et al., 2020; Wiersma et al., 2011). Neuroticism, extraversion, worry, rumination, and anxiety sensitivity predicted the course of anxiety symptoms (R^2 < 6%), although none of these factors was a unique predictor (Spinhoven, Batelaan, et al., 2016), which is often an indication of multicollinearity, also suggested by their substantial intercorrelations.

At baseline participants with a primary diagnosis of bipolar disorder had been excluded from NESDA. Mesbah and colleagues (2019) identified risk factors for the emergence of (hypo)manic episodes and symptoms (using the MDQ) in patients initially diagnosed with anxiety or depressive disorders. They identified high neuroticism (HR= 1.70) and low agreeableness (HR= 0.52) as predictors of the incidence of (hypo)manic episodes (N = 31/1888, 1.6%) or symptoms (233/1319, 18%) within the follow up period two to seven years after the baseline assessment. Once concomitant psychopathology and childhood adversity (HR = 0.77) were considered, only low agreeableness showed independent predictive validity. Thus, participants who developed (hypo) manic episodes described themselves as less cooperative, likeable, and unwilling to follow advice than those who did not develop (hypo)manic episodes.

The strong overlap of risk factors surfaced in the multivariate analyses in which more specific risk factors stopped being predictive of anxiety and depression when neuroticism was part of the model. For example, experiential avoidance predicted the onset, recurrence, and maintenance of depressive disorders over four years (Spinhoven, Drost, et al., 2016), but this relationship was fully explained by neuroticism, rumination, and worry. Also, the predictive validity of anxious and depressed self-associations for the onset of anxiety disorders over the next two years strongly attenuated once neuroticism and baseline anxiety and depression symptoms were part of the model (Glashouwer et al., 2011). There were, however, also specific risk factors that showed prognostic relationships that were independent of neuroticism such as differences in cognitive reactivity (Kruijt et al., 2013) and implicit self-esteem (van Tuijl et al., 2020).

2.1.3. Concluding remarks

Most personality risk factors were shared across anxiety and depression diagnostic categories (i.e. transdiagnostic), especially neuroticism, whereas some other personality risk factors showed relationships with specific symptoms of affective disorders, such as low extraversion or sociability. The personality risk factors showed strong correlations, also with external locus of control, hopelessness, rumination, worry, experiential avoidance, and fearful avoidance, which suggests that they cover similar phenotypic trait space and rely on shared machinery. The studies are in keeping with the broader literature that identified personality differences as the strongest available psychological predictors of future anxiety and depression problems. The NESDA results were consistent with the idea of a "healthy personality" with low neuroticism and relatively high levels of extraversion, conscientiousness, agreeableness, and openness (Bleidorn et al., 2020), as these participants were least likely to develop affective problems. Finally, the

correlated changes between personality scores and occurrence, remission, and persistence of affective disorders over time underscores their co-development.

2.2. Locus of control

Locus of control (LoC) is a personality construct that combines mastery and perceived constraints. To index LoC within NESDA, the Pearlin mastery scale was used (Pearlin and Schooler, 1978). A lower score indicates a more externally oriented LoC, the belief that outcomes in one's life are mainly due to chance or fate, whereas higher scores reflect a more internally oriented LoC, when one feels able to influence actions, other persons, and situations (mastery). LoC proved to be rather stable over up to nine years (Hovenkamp-Hermelink et al., 2019; Struijs et al., 2020), with NESDA participants becoming slightly more internally oriented over time (Hovenkamp-Hermelink et al., 2019; Hovens et al., 2016).

2.2.1. Cross-sectional associations

To provide some insight into the associations between the psychological vulnerability markers in NESDA; at baseline, more external LoC was positively associated with neuroticism (r=0.57), hopelessness (r=0.54), rumination (r=0.43), worry (r=0.54), anxiety sensitivity-physical concerns (r=0.19), anxiety sensitivity-social cognitive concerns (r=0.40), and negatively with extraversion (r=-0.41; Struijs et al., 2018). More external LoC was associated with more intense depressive symptoms (Struijs et al., 2013). This relationship was specifically carried by the cognitive symptoms of depression. Participants with an anxiety and/or depression disorder diagnosis showed lower scores on the mastery scale (i.e, external LoC) than participants without a history of affective disorders (Kok et al., 2017; Vlasveld et al., 2013), whereas remitted respondents scored between these two groups (Vlasveld et al 2013). The baseline data of individuals diagnosed with depression disorder in the past year showed that a more external LoC was also associated with more chronicity of depression (Wiersma et al., 2011). A study restricted to individuals diagnosed with panic disorder showed that LoC scores did not differ between subtypes of panic disorder (Pattyn et al., 2015).

2.2.2. Longitudinal relationships

External LoC showed independent predictive value for depressive symptoms at one-year follow up (Struijs et al., 2013); notably this predictive relationship was restricted to the cognitive symptoms of depression. In addition, participants with a more external LoC generally showed a relatively unfavorable course of affective disorders over 2-9 years (range of odds 1.25-1.45) in terms of chronicity of anxiety and depression disorder diagnoses as well as symptom severity (Hovenkamp-Hermelink et al., 2019; Struijs et al., 2018), despite adjustment for their mutual overlap, thus an external LoC proved to be a generic risk factor for affective disorders.

Two studies showed that LoC might also play a role in the impact of (self-reported) stressful life situations on (the course of) anxiety and depression symptomatology. One study showed that more external LoC mediated the relationship between childhood maltreatment and more intense symptoms of anxiety/depression as well as lower remission rates of anxiety and/or depressive disorder diagnosis at four year follow up (Hovens et al., 2016). The other study indicated that external LoC predicted higher anxiety and depression severity, but was unrelated to the incidence of positive and negative life-events (Hovenkamp-Hermelink et al., 2019). Meanwhile, more negative life-events in those with relatively high depression severity showed a prospective relationship with more external LoC, whereas more positive life-events were associated with more internal LoC. This unidirectional prospective association between life events and LoC is consistent with the view that LoC might be an important moderator/mediator of the link between experienced stress and the severity of depression symptoms. Accordingly, these NESDA findings highlight the relevance of stress related changes in LoC as one of the mechanisms that may link stress experiences to changes in vulnerability for psychopathology.

2.2.3. Concluding remarks

The NESDA findings are consistent with the view that individuals with a more externally oriented LoC are more likely to show both anxiety and depression symptoms and disorders and an unfavorable (chronic) course, which makes LoC a transdiagnostic vulnerability. In addition, the findings suggest that negative stressful experiences promote the development of a more external LoC. Combined, this points on the relevance of stress-driven changes in LoC as a mechanism that can help explain how stressful experiences may increase risk of developing (chronic) affective disorders.

2.3. Approach and avoidance tendencies

Anxious individuals generally avoid perceived threats to reduce levels of fear or anxiety, while depressed individuals show reduced approach and increased avoidance motivation. Two broadband motivational systems are thought to be involved in the development of anxiety and depression (Gray, 1987). In NESDA these were measured using the BIS/BAS self-report questionnaire and the Approach-Avoidance Task (AAT). The AAT is a reaction time task in which participants had to push or pull pictures of various emotional expressions (e.g., angry, happy, fearful) as fast as possible based on the color (yellowish/greyish) of the pictures (Struijs et al., 2017).

2.3.1. Cross-sectional associations with anxiety and depression

Automatic approach-avoidance tendencies showed no consistent association with any psychiatric variable or between individuals with and without disorders (Struijs et al., 2017). In contrast, all patient groups showed medium to large differences in trait avoidance scores compared to individuals without (a history of) anxiety/depression. Whether these associations were independent of differences in neuroticism was not analyzed. BAS scores were largely unrelated to diagnostic status and only showed a small dose-response relationship with depressive symptom severity, in line with the aforementioned role of extraversion.

2.3.2. Longitudinal relationships with anxiety and depression

Stronger trait avoidance tendencies predicted increased risk of recurrence (OR=1.55) and chronicity (OR=1.31) of anxiety disorders also when statistically controlling for demographics and baseline affective disorders (Struijs et al., 2018). Trait avoidance was also associated with the recurrence and chronicity of comorbid disorders (OR=1.29). The associations between stronger trait avoidance tendencies and increased risk of onset and chronicity of depressive disorders were no longer significant when statistically controlling for demographics and baseline affective disorders.

2.3.3. Concluding remarks

Behavioral inhibition seems to be a transdiagnostic feature of affective disorders, and to be more pronounced in anxiety than depression, and predictive of disorder recurrence and chronicity. Computerized performance measures of avoidance tendencies using emotional facial expressions appeared unrelated to outcomes. Finally, we found little evidence for low trait approach tendencies as a risk factor for the development of anxiety and depression.

3. Cognitions

3.1. Repetitive negative thinking and experiential avoidance

Repetitive negative thinking (RNT) comprises repetitive and intrusive thoughts, and a persistent focus on one's problems or negative

experiences (Ehring and Watkins, 2008). Measures of RNT typically focus on disorder-specific content such as worrying about future threats in anxiety, and rumination about past experiences in depression. Experiential avoidance captures unwillingness to remain in contact with aversive private experiences and avoidance of aversive experiences or eliciting cues (Hayes et al., 1996). Experiential avoidance has been associated with psychological constructs such as worry and rumination based on the presupposition that these mechanisms are strategies to avoid the overwhelming affect associated with specific thought content (Borkovec, 1994; Moulds et al., 2008).

3.1.1. Cross-sectional associations with anxiety and depression

RNT and experiential avoidance showed a moderately strong ($r > .5$) interrelationship, and showed cross-sectional relationships with symptoms of anxiety and depression, as well as with other psychological risk factors (e.g., neuroticism) (Spinhoven, Drost, et al., 2016; Struijs, Lamers, Spinhoven, et al., 2018). Moreover, a latent factor that combined RNT with worry, rumination, and perseverative thinking associated with depressive and anxiety disorders and their comorbidity. In concordance with the strong cross-sectional relationship between rumination and depression (Drost et al., 2012; Wiersma et al., 2011) and between worry and GAD (Drost et al., 2012), both independent of neuroticism, the unique portion of rumination showed a significant relationship with MDD and depressive comorbidity, and the unique portion of worry with GAD (Spinhoven, Drost, et al., 2015). Rumination and worry also showed concurrent associations with alcohol dependence (Boschloo et al., 2013), and rumination with evening chronotype (Solis et al., 2017), but not with cortisol awakening response (van Santen et al., 2011)..

3.1.2. Longitudinal relationships with anxiety and depression

In univariate analyses, worry, rumination, and experiential avoidance were risk factors for the onset, persistence, and recurrence of anxiety and depressive disorders over four-year follow-up (Spinhoven et al., 2016, 2017). This predictive effect became greatly attenuated in multivariate analyses statistically controlling for demographics, baseline symptoms, and neuroticism. The predictive properties of rumination and worry were independent of experiential avoidance, whereas the predictive value of experiential avoidance was not independent of rumination and worry (Spinhoven et al., 2016). Moreover, rumination predicted more persistent depression over 2-6 years, while worry was most strongly associated with persistent GAD (Struijs et al., 2018). The predictive power of rumination and worry on different course trajectories of anxiety disorders was also examined using a data-driven method based on life chart data of anxiety and avoidance symptoms (Spinhoven, Batelaan, et al., 2016). Symptoms of anxiety and avoidance persisted in 25% of the participants and slightly increased over six-years follow-up, while 7% reported a severe deterioration of symptoms. These unfavourable course trajectories were predicted by higher baseline levels of worry but not rumination. Yet, worry predicted no incremental variance in affective disorders once neuroticism, extraversion, anxiety sensitivity, and rumination were considered. Finally, rumination but not worry predicted onset of PTSD during a four-year follow-up, also when statistically controlling for demographic and clinical history variables, as well as psychiatric diagnoses at baseline (Spinhoven, Drost, et al., 2015).

3.1.3. Relationships with comorbidity of affective disorders

Longitudinal studies identified RNT or experiential avoidance as predictive of the onset, persistence, and recurrence of both anxiety and depressive disorders, which does not imply that RNT must be a causative factor of (i.e. mediates) their (developing) comorbidity. However, several NESDA studies suggest that high baseline RNT and experiential avoidance are implicated in the increasing comorbidity among anxiety disorders (social anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without panic) and depressive disorders (MDD, dysthymia, GAD) two years later (Spinhoven et al., 2014), and their prospective cross-disorder relationships. Baseline anxiety disorders predicted changes in depressive disorders over four years, which was partly mediated by changes in worry and rumination two years after baseline. The association between baseline depressive disorders and changes in anxiety disorders was mediated by changes in rumination but not by changes in worry (Drost et al., 2014).

Similar results were found when investigating content-independent RNT, with baseline anxiety disorders predicting individual depressive disorders and vice versa over four years, while these prospective associations were significantly mediated by level of RNT as assessed two years after baseline (Spinhoven et al., 2018). Similar analysis with experiential avoidance as putative mediator of comorbidity yielded comparable results with experiential avoidance two years after baseline mediating the prospective association of baseline anxiety disorders with depressive disorders four years later and vice versa (Spinhoven et al., 2014).

3.1.4. Concluding remarks

These NESDA findings strengthen the proposed relevance of negative repetitive thinking and experiential avoidance in the persistence and recurrence of affective disorders. The findings are also consistent with the presupposition that rumination, worry, and experiential avoidance share the tendency to engage in cognitive and behavioral avoidance in order to avoid personally threatening thoughts and accompanying negative emotions. This, common feature is associated with neuroticism and can be seen as a partly independent transdiagnostic risk factor implicated in the onset, course, and comorbidity of anxiety and depressive disorders.

3.2. Cognitive Reactivity

People differ in their probability of developing an anxiety- or depressive disorder in the presence of adversity and chronic stress. One potential explanation comprises ‘anxiety sensitivity’ (AS) and ‘cognitive reactivity’ (CR) to sad mood. AS captures the extent to which emotional or cognitive processes are activated by anxiety-relevant cues, such as bodily sensations. AS was measured with the Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992; S. E. Taylor and Stanton, 2007). This is an index of ‘reactivity’ – it does not assess the presence of certain thoughts and emotions in general, but their activation in response to a stressor (e.g., “It scares me when my heart beats rapidly”). High AS scores are associated with anxiety disorders (Taylor et al., 2007), suicidality (Capron et al., 2012) and substance abuse (Dixon et al., 2014; Schmidt et al., 2007; Zvolensky et al., 2009).

Cognitive reactivity to sad mood (CR) is the extent to which dysfunctional, depressogenic cognitions are activated by mild states of dysphoria (Teasdale, 1988). CR is typically measured by assessing negative cognitions with the Dysfunctional Attitudes Scales (DAS; Weissman, 1979) before and after the induction of a sad mood. The DAS change score reflects CR (Miranda et al., 1998). However, basic psychometric properties of DAS change scores, such as test-retest reliability, are unknown. Also, the DAS is not very sensitive to change, so mean DAS change scores are typically quite low. To overcome these limitations, the Leiden Index of Depression Sensitivity (LEIDS) was developed (Van van der Does, 2002; Solis et al., 2017) to measure CR without the use of mood induction using conditionally phrased items (e.g., “When I feel down, I am more bothered by perfectionism”), similar to the ASI.

3.2.1. Cross-sectional associations with anxiety and depression

Cognitive reactivity indices are moderately correlated with other psychological risk factors such as neuroticism, extraversion, locus of control and worry ($r = .32$ to $.61$) and were all associated with specific disorders, over and above the variance explained by personality traits neuroticism and extraversion (Drost et al., 2012). AS was specific to panic disorder and social anxiety disorder, whereas the CR subscales

aggression reactivity and rumination were unique to dysthymia and depression (Drost et al, 2012). The finding that recovered-depressed patients have higher LEIDS(-R) scores than never-depressed individuals was already quite robust at the start of NESDA. NESDA showed that chronicity was associated with higher LEIDS-R scores (Wiersma et al. 2011) and that remitted depressed patients with multiple episodes had higher scores than participants who remitted from a single episode (Elgersma et al., 2013). This "dose-response" relationship is consistent with the view that high CR puts people at risk for recurrent depression and is less relevant for the development of an incidental depressive episode.

3.2.2. Longitudinal relationships with anxiety and depression

NESDA showed that in never-depressed individuals, high CR scores predicted the first onset of depression over a period of two years (Kruijt et al., 2013). Furthermore, high scores on the rumination subscale during remission predicted faster recurrence (Figueroa et al., 2015).

Psychological risk factors that theoretically were specific to certain disorders indeed selectively predicted the course of these disorders. AS was associated with chronicity of panic disorder and social anxiety disorder, whereas CR as indexed by the rumination subscale of the LEIDS was associated with chronicity of depression (Struijs et al., 2018). Over a period of nine years, the temporal stability of CR measures was high and comparable to the temporal stability of personality traits such as neuroticism and LoC (Struijs et al., 2020). This pattern of results supports the notion of specific next to transdiagnostic predictors of the course of affective disorders, and is consistent with hierarchical models of psychopathology (Drost et al., 2014; Spinhoven et al., 2017; Spinhoven, Drost, et al., 2015, 2016).

The CR profile (LEIDS-R subscale scores) during remission also associated with the symptom profile during the prior depressive episode. People who were suicidal during their depressive episode, for example, reported more hopelessness during remission than their remitted peers without suicidal thoughts (Antypa et al., 2010). In other words, suicidal thoughts remain especially easily triggered after a depressive episode. This is an important finding for clinicians and patients to be aware of.

3.2.3. Concluding remarks

The finding that CR scores predicted the incidence of depression in never-depressed individuals (Kruijt et al., 2013) is the most novel NESDA finding of this section. It is important both from a clinical and a theoretical perspective. It is one of the first papers to demonstrate a cognitive vulnerability prior to a first depressive episode, in a longitudinal design. The finding that CR seemed especially relevant for the onset of multiple episodes and predictive of a chronic course further underlined its clinical relevance. Cognitive reactivity as indexed by the LEIDS and ASI demonstrated cross-sectional relations with anxiety- and depressive disorders and showed differential predictive validity for the onset, chronicity, and recurrence of both anxiety and depression. Both cognitive reactivity indices share common aspects and strongly suggest that emotional and cognitive processes activated by relevant cues are relevant to understanding affective disorders.

4. Implicit measures

4.1. Disorder-specific self-associations

Dysfunctional self-schemas are assumed to play a causal role in both anxiety disorders and depression (Beck and Haigh, 2014). According to current information-processing models, it is important to differentiate between 'explicit' (self) beliefs and automatic (self) associations (Gawronski and Bodenhausen, 2006). Explicit beliefs stem from the weighting of propositions and their corresponding 'truth' values, while automatic associations reflect more simple associations in memory that are difficult to control and do not require conscious reflection to influence affect, cognition, or behavior. Both types of associations are assumed to have different functional properties and both may be involved in affective disorders.

Thus far, most studies into self-schemas in affective disorders focused on consciously accessible traces of self-schemas and predominantly relied on self-report measures. To complement these 'explicit' findings and more directly tap into self-schemas, NESDA included adapted versions of the Implicit Association Task (IAT; Greenwald et al., 1998) as performance based implicit measures of automatic self-associations (Egloff and Schmukle, 2002). The IAT is a computerized reaction time task designed to measure the relative strengths of automatic associations between two contrasted target concepts and two attribute concepts. The implicit measures proved reliable, as indexed by Spearman-Brown corrected correlations between test halves (between .84 and .92).

4.1.1. Cross-sectional associations with anxiety and depression

Cross-sectional findings provided evidence for disorder-specific automatic and explicit self-associations (Glashouwer and de Jong, 2010). Furthermore, automatic (and explicit) self-anxious/depressed associations partly remained following remittance. Moreover, consistent with the view that automatic and more deliberate self-associations may be play a complementary role in affective disorders, it was found that both types of self-associations showed (partly) independent associations with the severity of symptoms of anxiety and depression (Wave 1: Glashouwer and de Jong, 2010; Wave 3: Jabben et al., 2014).

Automatic self-depressive and self-anxious associations also showed a partly independent relationship with suicidal ideation and attempts (Glashouwer et al., 2010). Although automatic self-associations did not explain additional variance over and above explicit self-beliefs, the interaction between automatic and explicit self-associations did. This suggests that the probability of having suicidal thoughts/attempts was especially high for individuals who had depressive (anxious) self-associations at both the automatic and explicit level.

4.1.2. Longitudinal relationships with anxiety and depression

Both automatic and explicit self-anxious associations and self-depressive beliefs showed predictive validity for the course of anxiety- and depressive disorders. Individuals with relatively strong self-anxious associations showed a reduced chance of remission from anxiety during a two year follow up, whereas individuals with relatively strong self-depressive associations showed a reduced chance of remission from depression (Glashouwer et al., 2012) and a heightened chance for the development of depressive symptoms (Struijs et al., 2013). Explicit self-anxious associations and both explicit and implicit self-depressive associations remained significant when statistically controlling for severity of baseline symptoms.

There was no evidence that relatively strong automatic self-associations preceded the first onset of anxiety disorders at two year follow up (Glashouwer et al., 2011). Automatic and explicit self-anxious associations predicted the recurrence of anxiety disorders within a two year follow up period, but not incremental to baseline measurements of anxiety symptoms and phobic avoidance. Similarly, premorbid automatic and explicit self-depressive associations predicted the first onset of depression within a two-year time window (Kruijt et al. 2013), but not incremental to baseline symptom severity and self-reported cognitive reactivity. Supporting the view that self-depressive associations reflect a malleable risk factor, findings indicated that for those who remitted from depression both automatic and explicit self-depressive associations weakened from baseline to follow up (van Tuijl et al., 2018). Importantly, the (remaining) strength of explicit self-associations after remittance predicted recurrence risk within a four year time window. These associations showed a dose-response relationship (Elgersma et al., 2013; van Tuijl et al., 2018). Thus, self-depressed associations may become stronger following prolonged activation during depressive episodes, which may render individuals increasingly vulnerable for the development of future episodes.

4.2. Affective-evaluative self-associations (self-esteem)

4.2.1. Cross-sectional associations with anxiety and depression

Only the group of comorbid anxiety and major depression disorders showed lowered implicit self-esteem compared to individuals without a history of affective disorders (van Tuijl et al., 2016). This latter group also showed lowest explicit self-esteem. Explicit self-esteem was more generally lowered in individuals with anxiety disorders or depression disorders with scores of remitted/recovered individuals in between the symptomatic groups and the group without a history of affective disorders. Supporting the view that low self-esteem represents a malleable factor, especially for participants with major depression disorder, explicit self-esteem substantially increased following remission (van Tuijl et al., 2020).

4.2.2. Longitudinal relationships with anxiety and depression

Both explicit and implicit self-esteem were significant predictors of anxiety and depression recurrence within a three-year time window. When statistically controlling for baseline symptoms, neuroticism, and history of comorbid depression/anxiety (i.e., adjusted models), specifically implicit self-esteem still showed independent predictive validity for depression recurrence, whereas both low implicit and explicit self-esteem showed independent prognostic value for anxiety recurrence.

4.2.3. Concluding remarks

NESDA provided evidence for dysfunctional disorder-specific (automatic) self-associations in individuals with anxiety and/or depression disorders, whereas lowered implicit self-esteem seems restricted to individuals with comorbid anxiety and depression disorders. Both types of self-associations seem especially relevant for the persistence and recurrence of affective disorders.

4.3. Attentional bias in depression

Cognitive models of depression emphasize the role of biased processing of affective information in the development and chronicity of depression (De Raedt and Koster, 2010; Gotlib and Joormann, 2010). A difficulty to redirect attention away from negative, depression-relevant information (Koster et al., 2005) together with attentional avoidance of positive information (Winer and Salem, 2016) may give rise to a negative, self-reinforcing loop that hampers people's ability to correct overly negative views of themselves and the world. The Exogenuous Cueing Task (ECT) that has been used in previous research to measure attentional bias in depression (e.g., Koster et al., 2005) was also included in NESDA to assess Attentional Bias (AB) for negative (e.g., inferior, worthless) and positive (e.g., valued, powerful) attributes. To test the specificity of AB for depression-relevant negative information, also general threat words were included (e.g., dangerous, pain). To differentiate between early and late processes the ECT covered short and long presentation times (500 and 1250 ms) (cf. Koster et al., 2005). Reaction-time based measures of AB typically show low internal consistency (McNally, 2019). This also yielded for the AB measures in NESDA (with Cronbach's alpha close to zero) which may have hampered their sensitivity as a measure of individual differences.

4.3.1. Cross-sectional and longitudinal relationships with depression and comorbidity

There was no evidence for AB towards negative or away from positive attributes in participants with major depression disorder (without dysthymia or history of AD) or individuals with major depression and a comorbid anxiety disorder (Elgersma et al., 2018), nor for threat adjectives. Yet, there was weak evidence that patients who were remitted from depression did show a differential AB that was restricted to negative attributes for long duration trials (1250 ms). This maintained attention for negative information might reflect a heightened sensitivity for signals related to the impending threat of a new upcoming depressive episode. Longitudinal findings showed that this and other AB were however not associated with the recurrence of major depression disorder or increased depressive symptoms up to four year follow up (Elgersma et al., 2019).

4.3.2. Concluding remarks

There was no consistent evidence for AB towards negative or away from positive adjectives in strictly defined clinical groups with major depression, with or without a comorbid anxiety disorder. Thus, heightened AB for negative or a lowered AB for positive adjectives seems not critically involved in the maintenance of depression. Longitudinal analyses in participants who were remitted from a major depression indicated that AB for negative or positive adjectives is neither critically involved in the recurrence of depression.

5. Discussion

As summarized in Table 3, most psychological risk factors included in NESDA are cross-sectionally associated with both singular anxiety and depressive disorders as well as their comorbidity. The same holds for disorder recurrence and persistence, and to a lesser extent first onset of affective disorders. NESDA identified transdiagnostic factors that may help explain the high comorbidity between affective disorders and overlap in symptoms, and indications for partly overlapping disorder-specific risk factors, which support the relevance of distinct disorder categories and disorder-specific mechanisms. This suggests that treatments could aim at transdiagnostic mechanisms implicated in diagnosis (e.g. neuroticism Barlow et al., 2017; or self-esteem, see Korrelboom et al., 2012), and that such a general approach could be complemented with disorder/diagnosis-specific interventions addressing more specific mechanisms (e.g., mindfulness-based cognitive therapy for cognitive reactivity, see Kuyken et al., 2010). Within NESDA adults with low neuroticism and relatively high levels of extraversion, conscientiousness, agreeableness, and openness were least likely to develop affective problems, in line with the notion of a healthy personality profile (Bleidorn et al., 2020).

5.1. Cross-sectional associations of psychological risk factors with affective disorders

Almost all of the selected self-reported psychological risk showed cross-sectional relationships with the development and chronicity of singular and comorbid anxiety and depression disorders. Replicating earlier cross-sectional findings in this well-powered NESDA study that allowed for selection of well-defined clinical groups, including individuals who were remitted from anxiety and/or depression and/or with a comorbid profile.

As an important asset, NESDA not only relied on self-report measures but also included implicit performance-based measures of constructs that are central to cognitive models of emotional disorders but are not accessible to introspection (Bar-Haim et al., 2007; Beevers, 2005; McCabe et al., 2000). NESDA provided emerging evidence for dysfunctional disorder-specific (automatic) self-associations in individuals with anxiety and/or depression disorders, whereas lowered implicit self-esteem was restricted to individuals with comorbid anxiety and depression disorders. Both types of self-associations seem especially relevant for associations with the persistence and recurrence of affective disorders.

However, in contrast with promising earlier results (Koster et al., 2005) there was no consistent evidence for attentional bias towards negative or away from positive adjectives in strictly defined clinical groups with affective disorders. Also, automatic approach-avoidance of emotional facial expressions showed no relationship with affective disorders. Important results given the fact that both attentional bias and automatic behavioral tendencies never before have been studied on such a large scale in well-defined clinical samples.

Table 2
Psychometric and descriptive details of psychological risk factors assessed within NESDA.

Construct	Description	Measure	Waves	#	Items	CA	Mode
Basic personality dimensions							
Extraversion	Sociability, positive affectivity, energy.	NEO-FFI	1,3,4	21	12	0.78-0.84	SR
Conscientiousness	Disciplined, goal striving, adherence to principles	NEO-FFI	1,3,4	17	12	0.78-0.80	SR
Agreeableness	Likability, trust, cooperation and altruism	NEO-FFI	1,3,4	15	12	0.58-0.83	SR
Openness	Intellectual curiosity, need for variety, and progressive attitudes	NEO-FFI	1,3,4	15	12	0.63-0.78	SR
Neuroticism	Emotional instability, negative affect, doom	NEO-FFI	1,3,4	28	12	0.75-0.90	SR
Locus of Control	Internal (stable) versus external (fate) LOC. Only mastery was assessed.	PM	1,3,4,5,6	9	5	0.87-0.88	SR
Dispositional Optimism	Generalized positive expectations towards the future	LOT-R	4	1	6	0.87	SR
Impulsivity	Disinhibition, Thrill and adventure seeking, experience seeking, boredom susceptibility	SSS	4	1	32	0.56-0.86	SR
Approach and Avoidance		BIS/BAS	4,5	2	11		SR
	Behavioral inhibition	BIS	4,5	2	7		SR
	Behavioral activation	BAS	4,5	2	4		SR
	Approach	AAT	4,5	2			CT
	Avoidance	AAT	4,5	2			CT
Self-esteem	Global Self-esteem	RSES	5,6	2	10	0.92	SR
Cognitions							
Worry	unwanted, uncontrollable, aversive cognitive activity associated with negative thoughts and emotional discomfort (frequency/intensity). Worry engagement scale.	PSWQ	1,2,3,4,5,6	13	11	0.92-0.96	SR
Perseverative thinking	Content-independent measures of repetitive negative thinking	PTQ	5,6	2	15	0.97	SR
Experiential avoidance	Acceptance and Action	AAQ-I	3,4	3	9	0.69-0.74	SR
Hopelessness/Suicidality	reactivity (subscale)	LEIDS-r	1,3,4,5,6	11	5	0.82-0.93	SR
Acceptance / Coping	subscale	LEIDS-r	1,3,4,5,6	5	5	0.56	SR
Aggression	subscale	LEIDS-r	1,3,4,5,6	7	6	0.79	SR
Control / Perfectionism	subscale	LEIDS-r	1,3,4,5,6	6	6	0.61	SR
Risk aversion	subscale	LEIDS-r	1,3,4,5,6	6	6	0.67	SR
Rumination on sadness	subscale	LEIDS-r	1,3,4,5,6	17	6	0.70-0.93	SR
Anxiety sensitivity	Fear of Anx S_x because of beliefs of their perceived harmful physical, social, or cognitive consequences	ASI		7	16	0.87-0.98	SR
	* Physical concerns	ASI-phc	1,2,3,4,5,6	3	8	0.87-0.89	SR
	* Social cognitive concerns	ASI-scc	1,2,3,4,5,6	3	6	0.78-0.80	SR
Cognitive reactivity	Cognitive reactivity to sad mood	LEIDS-r	1,3,4,5,6	5	34	0.93	SR
Implicit measures							
Implicit self-anxious associations	* Self-Anxiety (D-measure)	IAT	1,3	4		.87†	CT
Implicit self-depressive associations	* Self-Depression (D-measure)	IAT	1,3	8		.82†	CT
Explicit self-anxious associations	* Trait-Anxiety	IAT	1,3	4	10	0.94	SR
Explicit self-depressive associations	* Trait-Depression	IAT	1,3	8	10	0.95	SR
Implicit affective self-associations	* Self-esteem (D-measure)	IAT	5,6	2		.85†	CT
Attention bias	Exogenous cueing task: negative, positive, threat, neutral	ECT	3,4	2			CT

Note. #= NESDA studies that used the construct. †= Spearman-Brown corrected correlations between test halves. **Wave 1**=Baseline. **AAT**=Approach Avoidance Task. **ASI**= Anxiety Sensitivity Index. **BIS=**Behavioral Inhibition System. **BAS**=Behavioral Activation System. **CA=** Cronbach Alpha. **CT=** Computerized Task**. ECT**=Exogene Cueing Task. **IAT**= Implicit Association Test. **LEIDS-r**= Leiden Index of Depression Sensitivity – revised. **LOT-R**= Life Orientation Test-Revised. **NEO-FFI**=Neuroticism-Extraversion-Openness Five-Factor Inventory. **PM**= Pearlin Mastery Scale. **PSWQ**= Penn State Worry Questionnaire. **PTQ**= Perseverative thinking questionnaire. **RSES**= Rosenberg Self-esteem Scale. **SR**= Self-report. **SSS**= Sensation Seeking Scale, abbreviated version.

Overall, psychological risk factors showed moderate to strong interrelationships, and most risk factors were associated with either both anxiety and depression or neither (see Table 3), highlighting the similarities rather than the differences between these two seemingly distinct diagnostic entities (Kotov et al., 2017). The NESDA research methodology allowed for important nuances to be made however, such as low extraversion and cognitive reactivity being more specific for depression and social anxiety, and avoidance tendencies being more prominent in anxiety compared to depression (Fricke and Vogel, 2020). Also, certain content-related aspects of repetitive negative thinking were linked to specific disorders (e.g., worry was more strongly related to GAD, whereas rumination was more strongly related to MDD (Spinhoven et al., 2018). Finally, disorder specific self-associations proved to be associated with specific disorders (e.g. self-anxious associations were stronger in anxiety disorders).

Some risk factors showed specific associations with comorbid anxiety and depression, such as higher neuroticism, habitual avoidance, repetitive negative thinking (RNT) and (implicit) self-esteem (ter Meulen et al., 2021), which is consistent with the view that disorder comorbidity may be more than the sum of its parts (Kleiman and Riskind, 2012).

5.2. Longitudinal associations of psychological risk factors with affective disorders

Thanks to the longitudinal design of NESDA it could be established that most of the candidate psychological risk factors were also associated with the development and recurrence/chronicity of singular and comorbid depression and anxiety disorders and corresponding symptoms (for an overview see Table 4). Several results should be highlighted in that regard.

NESDA showed that cognitive reactivity increases the risk of developing one's first full-blown depression episode, and to experience multiple episodes in a chronic course, which underlined its clinical relevance. Additionally, longitudinal NESDA findings suggest that (early and later) negative life events may promote the development of more external locus of control, thereby pointing to the relevance of stress related changes in locus of control as one of the mechanisms that may help explain how stress experiences may heighten the risk for developing (chronic) affective disorders. Furthermore, implicit self-esteem showed independent predictive validity for depression recurrence even when statistically controlling for baseline symptoms, neuroticism, and history of comorbid depression/anxiety, pointing to its relevance as a target for (preventive) interventions. Finally, NESDA showed that repetitive negative thinking is not only a risk factor for singular anxiety and depression disorders but also specifically for the development of comorbidity.

Psychological risk factors typically overlapped in their predictive qualities when simultaneously included in statistical models. However, some risk factors, such as cognitive reactivity, implicit and explicit self-esteem, and implicit and explicit self-depressive associations showed prognostic value for the development of anxiety and depression that was (partly) independent of other risk factors that were included in the models. Yet, although some risk factors failed to show incremental predictive value (over symptom severity and more general negative affectivity), this does not imply that these factors are no (possible) causal risk factors (Kraemer et al., 2001). More generally, statistically controlling for symptoms and general negative affectivity may over-adjust for the role of potential mechanisms in the etiology and course of depression and anxiety, and remove constituent components from the predictors themselves, such as the depression trait in neuroticism (Riese et al., 2016).

5.3. Treatment implications

As most psychological risk factors seem to be associated with affective disorders in general and are moderately to strongly intercorrelated, it can also be questioned whether it is fruitful to target individual psychological vulnerabilities associated with single depression or anxiety disorders. Their high interrelatedness suggests a common etiologic factor (Hong and Cheung, 2015) presenting an avenue for transdiagnostic interventions. The transdiagnostic model focuses on identifying the common psychological processes that underly a broad array of mental disorders (Harvey et al., 2004) and targeting these factors in treatment across disorders (Barlow et al., 2004). Recently Barlow and co-workers (2014) argued that the core psychopathological mechanism or functional relationship in depression, anxiety and related emotional disorders consists of intense negative emotional reactions as manifested by individuals with higher levels of neuroticism, and subsequent efforts to down-regulate these aversive negative emotional experiences. Such individuals may be more likely to engage in avoidant coping strategies (such as rumination, worry, emotion suppression, experiential avoidance, anxiety sensitivity) to manage their emotions, which paradoxically may increase the frequency/intensity of these negative emotions. Preliminary evidence shows that transdiagnostic treatments such as the Unified Protocol (UP) (Barlow, 2017) targeting these core mechanisms are superior to control conditions on anxiety, depression and quality of life (Newby et al., 2015). It is noteworthy, that most of the available evidence-based interventions for anxiety and depression are designed for single anxiety or depression disorder and are directed at modifying presumed specific mechanisms underlying these single disorders. Comparisons of the effectiveness of transdiagnostic with disorder-specific treatments remain rare and their comparative effectiveness in single and combined disorders is not well established.

Table 3
Overview of cross-sectional associations of psychological factors with (comorbid) anxiety and depression diagnoses.

	Outcome		
Construct	Anxiety†	Depression†	Comorbid
Personality dimensions			
Extraversion	+	++	+
Conscientiousness	+	++	+
Agreeableness	+	+	+
Openness	-	-	-
Neuroticism	+	+	+
Locus of Control	+	+	+
Dispositional Optimism	+	+	+
Approach and Avoidance			
BIS	++	+	+
BAS	–	++	–
AAT approach	–	–	–
AAT avoidance	–	–	–
Cognitions			
Worry	++	+	+
Perseverative thinking	+	+	+
Experiential avoidance	+	+	+
Rumination on sadness	+	++	+
Cognitive reactivity	+	++	+
Anxiety sensitivity	+	-	+
Implicit measures			
Implicit self-anxious associations	++	+	+
Implicit self-depressive associations	+	++	+
Implicit self-esteem	–	–	+
Explicit self-anxious associations	++	+	+
Explicit self-depressive associations	+	++	+
Explicit self-esteem	+	+	+
Attention bias		–	–

Note. – = no association found; + = (a majority of) positive result(s). † Whenever positive associations were found for both depression and anxiety, ++ is used to indicate whenever one association was stronger versus the other.

5.4. Limitations

Direct comparison of cross-sectional associations of psychological

Table 4
Overview of longitudinal associations of risk factors with (comorbid) anxiety and depression diagnoses.

	Anxiety			Depression			Comorbid		
Construct	FO	RC	PS	FO	RC	PS	D	RC	PS
Personality dimensions									
Extraversion	+	-/+	+	+	+	+	+	-/+	-/+
Conscientiousness	-/+	-/+	+	+	+	-/+	+	+	+
Agreeableness	-	-	+	+	-	-/+	+	-	-/+
Openness	-	-	-	-/+	-	-/+	-	-	-
Neuroticism	+	+	+	+	+	+	+	+	+
Locus of Control		+	+		+	+			
Dispositional Optimism									
Approach and Avoidance									
BIS		+	+		+	+		+	+
BAS		–	–		–	–		–	–
AAT approach		–	–		–	–		–	–
AAT avoidance		–	–		–	–		–	–
Cognitions									
Worry	+	+	+	+	+	+		+	+
Perseverative thinking		+	+		+	+		+	+
Experiential avoidance	+	+	+	+	+	+		+	+
Rumination on sadness	+	+	+	+	+	+		+	+
Cognitive reactivity				+	+	+			
Anxiety sensitivity			+			–			
Implicit measures									
Implicit self-anxious associations	–	–/+	–/+		–	–			
Implicit self-depressive associations	–	–	–	–/+	–/+	–/+			
Implicit self-esteem		+			+				
Explicit self-anxious associations	–/+	+	+		–	–/+			
Explicit self-depressive associations	–/+	–/+	–	–/+	+	+			
Explicit self-esteem		+			+				
Attention bias					–	–		–	–

Note. FO = First onset. **RC**= Recurrence. **PS** = Persistence. **D**=Development. – = no association found; -/+ = mixed results or association no longer significant after adjustment of covariates; + = (a majority of) positive result(s).

risk factors with affective disorders remained elusive because not all risk factors could be assessed in the same waves (see table 2). In addition, direct comparison is hampered by differences in selected subgroups and outcomes (e.g., symptoms or disorders), follow-up time, and number and type of predictors in the models. The risk factors that were studied showed conceptual overlap, and also, many NESDA research designs contrasted groups of participants with various levels of symptoms (or diagnoses) for (cross-sectional or longitudinal) group differences on the psychological vulnerabilities, which were sometimes implicitly assumed to reflect a causal process despite the notion these differences between groups could well reflect a scar or concomitant mental state (Haeffel et al., 2021). Finally, NESDA has been set-up in such a way that it favours examination of the course of affective disorders versus the onset of disorders by oversampling diagnosed participants at baseline, and some diagnoses of affective disorders (such as OCD and PTSD) were not represented in NESDA.

5.5. Conclusion

This narrative review of NESDA studies examining the specificity and predictive value of important candidate psychological risk factors showed that – barring attentional bias and automatic behavioral tendencies – all proposed risk factors have both cross-sectional and prospective relationships with the development and chronicity of singular and comorbid depression and anxiety disorders and corresponding symptom severity. Mostly transdiagnostic factors were identified such as high neuroticism, low implicit self-esteem and repetitive negative thinking. Additionally, there were indications for partly overlapping disorder-specific risk factors, which support the relevance of distinct symptom clusters and syndrome-specific mechanisms. Overall, results align with hierarchical models of psychopathology, in which conceptually broad psychological risk factors such as personality, repetitive negative thinking and habitual avoidance are grouped in higher order dimensions (e.g., an 'internalizing spectrum') and conceptually more specific risk factors are grouped in lower order syndromes (i.e., disorders, see Kotov et al., 2017, and Haeffel et al., 2021 for a critique). Together, the results point to the relevance of both transdiagnostic and disorder-specific psychological targets for therapeutic interventions.

Author statement

All authors contributed to conceptualization, writing, editing and revision of the manuscript, and all approved the final article. SS, PdJ and PS designed the study, and interpreted the data. SS and BJ prepared the tables.

Data availability

According to European law (GDPR) data containing potentially identifying or sensitive patient information are restricted; our data involving clinical participants are not freely available in a public repository. However, data are – under some specifications - available upon request via the NESDA Data Access Committee (nesda@ggzingeest.nl). See also our website: www.nesda.nl.

Author Disclosure

Role of the funding source

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific

Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).

Declaration of Competing Interest

All other authors declare that they have no conflicts of interest.

Acknowledgements

None.

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