Author's response to reviews

Title: Disorder-specific cognitive profiles in major depressive disorder and generalized anxiety disorder.

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Author's response to reviews: see over
Dear Dr. Alice Murray,

Please find enclosed a revised version of our manuscript ‘Disorder-specific cognitive profiles in major depressive disorder and generalized anxiety disorder’ (MS: 1942614638994144) for your consideration for publication in *BMC Psychiatry*.

We gratefully used your valuable comments and those of the reviewers to improve the quality of our manuscript. A more detailed description of these changes is provided in the point-by-point reply below and marked in the manuscript in red colored text. For instance, we revised the discussion so there is now a greater level of detail and an expansion of the limitations.

Overall we are pleased by, what we felt, a positive reception of our paper, and we would like to thank you and the reviewers for their time and effort put in reviewing our manuscript. We hope that this revision has brought our paper closer to meeting the standards for publication in *BMC Psychiatry*.

Yours sincerely,

Sanne Hendriks, MD
REVIEWER 1:

Comments:
This study compares several cognitive constructs in major depressive disorder (MDD) and generalized anxiety disorder (GAD) and reports that levels of hopelessness/suicidality and rumination were significantly higher in MDD, whereas anxiety sensitivity for physical concerns and pathological worry were significantly more prominent in GAD. Individuals with both MDD and GAD had “more extreme depression cognitions” compared to individuals with MDD and GAD alone and a “similar anxiety profile” compared to individuals with GAD alone. The authors conclude that these findings support the notion that MDD and GAD are distinct conditions and that they should be classified accordingly. I have a number of comments and suggestions, as follows:

1.01 Three instruments were used in the study, of which two (Anxiety Sensitivity Index [ASI] and Penn State Worry Questionnaire [PSWQ]) are very well known, whereas one (Leiden Index of Depression Sensitivity; LEIDS-R) is much less used. The authors might make a comment about the reason for choosing the latter and not choosing an alternative measure such as the Cognitions Checklist that they mention on page 11.

Re: The Cognition Checklist (CCL) is indeed an often used, valid and reliable instrument. However, research indicated that the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) is also a reliable and valid instrument to measure the cognitive reactivity to sad mood (Antypa et al, 2010; Booij and van der Does, 2007; Van der Does et al., 2002; Van der Does et al. 2005; Van der Does et al., 2008; Firk and Markus, 2009; Merens et al., 2005; Moulds et al., 2008; Williams et al., 2008). We believe the advantages of the LEIDS-R are the subdivision in different subscales and the conditional wording of the items. The LEIDS-R has 6 different subscales compared to the 2 subscales of the CCL (a depression and an anxiety subscale). Furthermore, the wording of the LEIDS-R is more similar to the wording of the ASI compared to the CCL. For instance, a typical CCL item is “I’m worthless”. An example of an item from the LEIDS-R is “When I feel down, I more often feel hopeless about everything”. An example of an item from the ASI is: “When I am nervous, I worry that I might be mentally ill”.

We added information about the validity and reliability of the LEIDS-R (page 7): In several studies the LEIDS-R has been found to be sensitive to depression history and they support the validity and the reliability of the LEIDS-R as a measure of depression vulnerability.
1.02 Also with regards to the LEIDS-R, the reported Cronbach alpha values (ranging from 0.56 to 0.82) were not convincing. The authors should make some comment about that and also about the acceptability of this instrument more generally.

Re: Please also see 1.01. We added the Cronbach alpha values for all subscales of the LEIDS-R and made a comment about these values (page 7): The Cronbach’s α for the LEIDS-R subscales was 0.82 for the subscale Hopelessness/Suicidality, 0.56 for the subscale Acceptance/Coping, 0.79 for the subscale Aggression, 0.61 for the subscale Control/Perfectionism, 0.67 for the subscale Risk Avoidance and 0.70 for the subscale Rumination. Overall, this suggests that the internal reliability of the subscale Acceptance/Coping is not very good, but that of all other subscales are acceptable to good.

1.03 It was unusual to use the ASI without two of its items and to administer the PSWQ without five items. Can authors justify this?

Re: Previous research on NESDA (Drost et al, in press) showed that to maintain good internal consistency of the ASI, factors were combined to form 2 factors: a physical concerns factor and a social-cognitive concerns factor. Items 7 and 13 were left out as both items showed very low loadings on each of the 2 factors and removal would improve the internal consistency. Removal of these two items did not affect the factor structure. We have clarified this in the paper (page 7): Previous research on NESDA\textsuperscript{[12]} showed that to maintain good internal consistency factors were combined to form 2 factors: a physical concerns factor and a social-cognitive concerns factor. Items 7 and 13 were left out as both items showed very low loadings on each of the 2 factors and removal would improve the internal consistency. Factor analyses in previous research showed that a two-factor solution provides a better fit (Fresco et al., 2002; Brown, 2003). Factor 1 (Worry Engagement) demonstrated higher internal consistency (higher Cronbach’s α values) and significantly stronger correlations compared to the total PSWQ score and factor 2 (Absence of Worry). For this reason, the research team who set up the Netherlands Study of Depression and Anxiety (NESDA) choose to include the PSWQ questionnaire that contained the 11 items of Worry Engagement. We have clarified this in the paper (page 8): Factor analyses in previous research showed that a two-factor solution provides a better fit.\textsuperscript{[47,48]} Factor 1 (Worry Engagement) demonstrated higher internal consistency and significantly stronger correlations compared to the total PSWQ score and factor 2 (Absence of Worry). For this investigation, we used the questionnaire that contained the 11 items of Worry Engagement.
1.04 The authors only report frequencies of co-occurring panic disorder and social phobia. What about other co-occurring disorders, for example posttraumatic stress disorder and specific phobia? Was there any other psychopathology, such as personality disorders or eating disorders? It is important to provide data about other co-occurring conditions because they might have affected the scores on the instruments used in the study.

Re: It is indeed important to provide data about other co-occurring conditions. Participants were excluded when they had a clinically overt primary diagnosis of severe other psychiatric disorders, such as e.g. psychotic, obsessive compulsive, bipolar or severe addiction disorder. Therefore, it is not likely that severe other psychiatric disorders are very prevalent. We did not formally test the presence of specific phobia, personality disorders and eating disorders in the NESDA study. We changed the limitation section so that this limitation is explicit mentioned (page 14): subjects were excluded when they had a clinically overt primary diagnosis of severe other psychiatric disorders such as psychotic, obsessive compulsive, bipolar or severe addiction disorder. However, some other conditions may have been present which were not further assessed, such as posttraumatic stress disorder, specific phobia, personality disorder or eating disorder. Consequently, we could not examine the full range of comorbidity among GAD and MDD in more detail.

1.05 Discussion is rather “thin” and would benefit from less repetitiveness and a more thoughtful examination of the issues. In particular, the authors do not discuss in sufficient detail the reasons for discrepant findings between studies.

Re: Please also see 1.06, 1.07 and 1.08. We revised most of the discussion and we hope we have taken away the concerns of the reviewer.

1.06 This study’s findings can also be interpreted as suggesting that there were more similarities between MDD and GAD than there were significant differences. Table 2 shows that MDD and GAD individuals did not differ significantly with respect to the scores on acceptance/coping, aggression, control/perfectionism, risk aversion and anxiety sensitivity for social-cognitive concerns (5 subscales), with significant differences being found on the scores on hopelessness/suicidality, rumination, anxiety sensitivity for physical concerns and pathological worry (4 scales/subscales). How does this support the notion that MDD and GAD are distinct?

Re: We agree with the reviewer that besides the differences in cognitive domains there are several parallels as well. Therefore, we revised these parts of the discussion and underline the commonalities in cognitive profiles in MDD and GAD. For example (page 11): Furthermore, most subscales showed similar results for MDD and GAD. However, despite
these commonalities in cognitive profiles in MDD and GAD, there are significant differences between the disorders, which we think are important characteristic for the disorders. We found that hopelessness/suicidality and rumination are more common in MDD whereas physical concerns and pathological worry are more common in GAD. These findings are in line with previous research, and seem to fit in models like the cognitive content-specificity model and the tripartite model of anxiety and depression. We hope we have given sufficient support for our notion in the discussion.

1.07 The pattern of results for individuals with both MDD and GAD is clearer and may suggest that this co-occurrence denotes a more severe illness. Again, a more detailed discussion of this is missing.

Re: We added the following paragraph to the discussion (page 13): *The cognitive profile of comorbid MDD/GAD showed more extreme depression cognitions than both single disorders, and a comparable anxiety profile compared to GAD. These results may suggest that comorbidity between MDD and GAD denotes a more severe illness since previous research showed that severity is strongly related to comorbidity.*[2] As mentioned before, depression and anxiety have notably high rates of comorbidity. Cognitive constructs may shed some light on the issue of comorbidity but also other factors seem important. For example, previous research showed a systematic link between personality traits and psychopathology.[70] Possibly, personality traits may serve as vulnerability factors or may be the underlying cause of a disorder. For instance, neuroticism/negative emotionality (stress reactivity and a tendency to experience negative emotions) has shown to be elevated in both depressive and anxiety disorders and consequently could contribute to comorbidity among them.[70]

1.08 The authors note that their results show that “rumination is specific for MDD whereas worry is specific for GAD” (p. 11). This is a definitive statement, which does not follow from the results: a significantly higher mean score on a measure of pathological worry in individuals with GAD does not automatically mean that pathological worry is specific for GAD, and the same applies to rumination and MDD. More thought should be put into a discussion of the similarities and differences between pathological worry and ruminations and findings of this study need to be compared to those of previous research.

Re: We agree with the reviewer and have expounded these statements. We revised this paragraph and gave more review of the literature (page 11-12): *Our results showed that rumination is more prominent in MDD whereas worry is more prominent in GAD. Although our findings are much in line with previous studies,[53-55] the assertion that worry only relates*
to anxiety and rumination only to depression has been challenged. Worry has been found to be associated with depression, and rumination with anxiety.\[^{37,56-58}\] There is a general consensus that rumination and worry share some degree of overlap. However some researchers argue how similar rumination and worry are. Rumination has been found significantly correlated to worry.\[^{58,59}\] Furthermore, Segerstrom et al. (2000)\[^{59}\] found that both rumination and worry are forms of repetitive thinking. Watkins et al. (2005)\[^{60}\] examined differences and similarities between rumination and worry and found very few differences. One difference in their study was the temporal content of the intrusive thoughts. Worry thoughts were more concerned with the future and less concerned with the past than ruminative thoughts which was in line with previous research.\[^{55}\] So it seems that rumination is oriented towards the past and is stronger associated with depression, while worry is oriented towards the future and is stronger associated with GAD.

REVIEWER 2:

Comments:
This study examined cognitive factors that would distinguish between depression, GAD, and mixed depression/GAD, based on the tripartite and cognitive content-specificity models of anxiety and depression. Participants were recruited as part of the Netherlands Study of Depression and Anxiety (NESDA). In multivariate analyses, individuals with major depression (MDD) were distinguished from those with generalized anxiety disorder (GAD) by higher scores on a measure of hopelessness/suicidality and rumination, and by lower pathological worry and anxiety sensitivity involving physical concerns. MDD was distinguished from comorbid MDD/GAD by lower pathological worry, and GAD was distinguished from comorbid MDD/GAD by lower hopelessness/suicidality, rumination, anxiety sensitivity involving social concerns, and by higher anxiety sensitivity involving physical concerns.
This study has the potential to contribute to the literature on cognitive distinctions between GAD and MDD and is relevant, given recent discussions leading to DSM-V on whether or not to classify GAD with MDD. The study has several strengths, including sample size, comparison of “pure” GAD and MDD to comorbid MDD/GAD, and assessment of cognitive constructs previously found to distinguish between depression and anxiety. Analyses also adjusted for panic disorder and social phobia.
The following are suggestions for improving the manuscript:
2.01 The paper is written as if DSM-V is not yet out. It should be revised in light of the fact that DSM-V has been released.

Re: We revised the paper in light of the fact that DSM-5 has been released (page 15): The classification of MDD and GAD was under scrutiny in the process leading to DSM-5 and there has been a number of calls to reclassify GAD in the same category as MDD (“the distress disorders”). Early GAD definitions suffered considerably from low reliability and poor validity. However, worry became the essential feature of GAD in DSM-III-R. DSM-IV further clarified the diagnosis by focusing on physical symptoms around chronic levels of tension and removing symptoms that more likely reflect acute autonomic arousal. These changes increased the diagnostic reliability and helped to distinguish GAD from other anxiety and mood disorders and demonstrated unique mechanisms and patterns of impairment. This is an important reason why MDD and GAD are still represented as distinct disorders in DSM-5.

2.02 The introduction should add more review of the literature on the tripartite and cognitive content specificity models and include more recent studies.

Re: We added more review of the literature on the tripartite and cognitive content specificity models and included more recent studies (page 3-4): Despite the commonalities between MDD and GAD there are also distinguishing factors. Some research, for instance, gave indications that there are differences in cognitive profiles. Models have been developed to explain these differences in cognitions, for example the cognitive content-specificity model and the tripartite model. The cognitive content-specificity model postulates that depressed individuals and anxious individuals differ in their maladaptive thought content. Depressive thought content reflects themes like negative evaluations of the self, the world, and the future, whereas anxious thought content reflects only future-oriented concerns with an anticipation of physical or psychological threats and an inability to cope. In the tripartite model of anxiety and depression, negative affect is proposed to be associated with both anxiety and depression, whereas lack of positive affect is viewed as specific to depression and physiological hyper-arousal is viewed as specific to anxiety. In a revised version of the tripartite model each disorder contains a general, a specific, and a unique component. The general component refers to a factor that anxiety and depressive disorders have in common, the specific component is shared with certain disorders but not all, and the unique component is a characteristic of a particular disorder differentiating it from all the others. Many studies have investigated aspects of the cognitive content-specificity model and the tripartite model. Previous research showed that the constructs of the cognitive content-specificity model and the tripartite model are meaningfully correlated, and that the integration of the models may better discriminate between anxiety (high negative
affect and anxious cognitions) and depression (high negative affect, low positive affect, and depressive cognitions) than either model alone.\textsuperscript{[25-27]}

2.03 Need more specificity on the types of depressive and anxious cognitions to which the authors are referring in the studies reviewed in the third paragraph and also better review of the literature on the relation between these cognitions and depression/anxiety.

Re: We revised this paragraph and gave more specificity on the types of depressive and anxious cognitions and tried to give a better review of the literature (page 4): So overall there are suggestions for an overlapping shared latent structure behind GAD and MDD as well as for distinct underlying cognitive vulnerabilities as described in e.g. the tripartite and cognitive content-specificity models. Research on depression and anxiety cognitions across MDD and GAD shows inconsistent findings. A meta-analysis of Naragon-Gainey\textsuperscript{[28]} showed that anxiety cognitions were significantly higher in individuals with GAD compared to individuals with MDD. GAD had a strong association with anxiety sensitivity (tendency to fear anxiety-related sensations) and was related to physical (fear of physical sensations of anxiety), cognitive (fear of mental incapacitation or cognitive dyscontrol), and social concerns (fear of public observation of anxiety). Depression was moderately associated with anxiety sensitivity and was specifically related to cognitive concerns. However, another meta-analysis,\textsuperscript{[20]} in which the cognitive content-specificity hypothesis was evaluated, showed that depression cognitions (mainly measured by the cognitions checklist, i.e. thoughts of loss and failure) are specific to depressive symptomatology, anxiety cognitions (mainly measured by the cognitions checklist, i.e. thoughts of harm and danger) show no such specificity and are associated with both depressive and anxious symptomatology in a similar way. These findings were generally inconsistent with the cognitive content-specificity hypothesis. Also Yook et al.\textsuperscript{[29]} found no significant differences between MDD and GAD in anxiety symptoms and pathological worry, which is a major symptom of GAD (American Psychiatric Association, 1994). Furthermore, Beck et al. (2001)\textsuperscript{[25]} found that worry is correlated with high negative affect and both are shared in depression and anxiety. Their results gave also support that hopelessness is correlated with low positive affect, and is a unique component of depression.

2.04 In the method section, it would be useful to include the number of items in each subscale of the LEIDS-R, along with Cronbach’s alpha for each subscale, given the wide range (from .56-.82). This is important, given that the anxiety-related scales seem to have more adequate alpha levels, which may impact the findings.
Re: We added the number of items and the Cronbach alpha values for all subscales of the LEIDS-R and made a comment about these values (page 7): The Leiden Index of Depression Sensitivity (LEIDS-R)[41-43] is a self-report measure of cognitive reactivity to sad mood. The LEIDS-R has 34 items scored on a 5-point Likert scale ranging from “0=not at all” to “4=very strongly” and covers six subscales. Subjects were asked to indicate whether and how their thinking patterns change when they experience mild dysphoria. The names of the subscales and sample items are: Hopelessness/Suicidality (5 items, for example: ‘When I feel sad, I feel more hopeless about everything’); Acceptance/Coping (5 items, for example: ‘When I am sad, I feel more like myself’); Aggression (6 items, for example: ‘When I feel down, I lose my temper more easily’); Control/Perfectionism (6 items, for example: ‘When I am in a sad mood, I become more bothered by perfectionism’); Risk Avoidance (6 items, for example: ‘When I feel down, I take fewer risks’); Rumination (6 items, for example: ‘When I feel sad, I spend more time thinking about the possible causes of my moods’). In several studies the LEIDS-R has been found to be sensitive to depression history and they support the validity and the reliability of the LEIDS-R as a measure of depression vulnerability.[41-48] The Cronbach's $\alpha$ for the LEIDS-R subscales was 0.82 for the subscale Hopelessness/Suicidality, 0.56 for the subscale Acceptance/Coping, 0.79 for the subscale Aggression, 0.61 for the subscale Control/Perfectionism, 0.67 for the subscale Risk Avoidance and 0.70 for the subscale Rumination. Overall, this suggests that the internal reliability of the subscale Acceptance/Coping is not very good, but that of all other subscales are acceptable to good.

2.05 Age, gender, and education, which are presently at the beginning of the results section, should go in the method section with the description of the sample. In addition, the description of the sample should include number of participants in the final sample (and number in each group), even though this is included in Table 1. Re: We added information on age, gender, and education to the sample description. The method section now states (page 6): The Composite Interview Diagnostic Instrument (CIDI version 2.1)[40] was used to diagnose mental disorders, including MDD and GAD. For the present study, we included subjects with 6-month MDD, GAD, and comorbid MDD/GAD diagnoses. In total 1028 subjects were included: 655 with MDD, 107 with GAD and 266 with both MDD and GAD. The mean age of the study sample was 41.6 years, 66.4% was female, and the mean of years of attained education was 11.9 years.
2.06 One limitation that was not addressed was the retrospective nature of the study. What the analyses did not address was whether the cognitive constructs examined were causes or consequences of the disorders. While not critical to the conclusions drawn, this issue should be mentioned in the discussion.

Re: We do acknowledge the limitations of the cross-sectional data and have added this to the limitation section (page 13-14): the cross-sectional study design precludes any causal interpretations regarding the cognitive profiles in MDD and GAD, and longitudinal studies are necessary to address such questions.

2.07 The authors should proofread the language in the paper. For instance, under the statistical analyses section, the sentence, “We analysed effect sizes as a standardized indication of the size of found contrasts…” is awkwardly worded and thus difficult to understand. There were a few other instances of awkward wording, and the authors should proofread.

We proofread the manuscript and we hope we have taken away the concerns of the reviewer.