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Latent anxiety in clinical depression is associated with worse recognition of emotional stimuli

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Abstract

Background: Major Depressive Disorder, characterized by cognitive affective biases, is a considerable public health challenge. Past work has shown that higher depressive symptoms are associated with augmented memory of negative stimuli. In contrast, anxiety symptoms have been associated with overgeneralization of emotional memories. Given the high comorbidity of depression and anxiety, it is critical to understand how cognitive affective biases are differentially associated with clinical symptoms.

Method: We used continuous measures of depression (Beck Depression Inventory [BDI-II]) and anxiety (Beck Anxiety Inventory [BAI]) to evaluate an adult sample ($N = 79$; 18–41 years old, 58 female). Emotional memory discrimination and recognition memory were tested using an emotional discrimination task. We applied exploratory factor analysis to questions from the BAI and BDI-II to uncover latent constructs consisting of negative affect, anhedonia, somatic anxiety, and cognitive anxiety.

Results: We report evidence that anxious symptoms were associated with impaired recognition of negative items after accounting for age and sex. Our exploratory factor analysis revealed that impaired negative item recognition is largely associated with somatic and cognitive anxiety factors.

Limitations: Interpretations in a mixed pathology sample, especially given collinearity among factors, may be difficult.

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Declaration of Competing Interest

We have no conflicts of interest to declare.

CRediT authorship contribution statement

Steven J. Granger: Conceptualization, Formal analysis, Visualization, Writing – original draft. **Joren G. Adams:** Conceptualization, Formal analysis, Visualization, Writing – original draft. **Sarah M. Kark:** Formal analysis, Visualization. **Mithra T. Sathishkumar:** Data curation. **Ivy Y. Chen:** Data curation. **Ruth M. Benca:** Visualization. **Liv McMillan:** Data curation. **John T. Janecek:** Formal analysis. **Michael A. Yassa:** Conceptualization, Visualization, Writing – original draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2022.01.009.

Conclusions: We provide evidence that somatic and cognitive anxiety are related to impaired recognition memory for negative stimuli. Future clinical investigations should uncover the neurobiological basis supporting the link between recognition of negative stimuli and somatic/cognitive symptoms of anxiety.

Keywords

Depression; Anxiety; Episodic memory; Pattern separation; Negative affect; Emotional memory

1. Introduction

Major depressive disorder (MDD) is one of the most pressing public health challenges facing our society today. As many as 17.3 million adults in the United States 18 years and older were thought to have at least one major depressive episode in 2017 (NIMH, 2017). Characterized by depressed mood, loss of pleasure or interest, fatigue, insomnia, and suicidal ideation, MDD is also highly comorbid with anxiety disorders (Mineka et al., 1998). As the prevalence of comorbidity of anxiety disorders with MDD may be as high as 60% of cases (Kaufman and Charney, 2000) an extensive effort is being made to take a more dimensional approach to understanding the comorbid profiles of these mental illnesses. Prior work has explored both the constructs of depression and anxiety in large clinical cohorts using exploratory factor analyses to uncover latent clusters of variables from the Beck Anxiety Inventory (BAI) and Beck Depression Inventory-II (BDI-II) scales. These investigations yield evidence of a tripartite model of depression and anxiety (consisting of negative affect, low positive affect, and physiological hyper-arousal) and theorize that while these constructs share general negative affect, they can perhaps be differentiated based on the basis of factors specific to each syndrome (Lee et al., 2018; Clark and Watson, 1991).

Cognitive affective biases have been well documented in MDD (Murrough et al., 2011; Chamberlain and Sahakian, 2006), can be detected even during remission and are associated with persistent psychosocial impairment (Conradi et al., 2011; Hasselbalch et al., 2011; Lam et al., 2014). Prior work has reported memory disturbances in depression and anxiety (Pittenger, 2013; Dillon and Pizzagalli, 2018; Leal and Yassa, 2018). Evidence has linked both MDD diagnosis as well as depressive symptom severity to augmented memory for negative items both in terms of recognition (Bai et al., 2017; Hamilton and Gotlib, 2008) and discrimination (Leal et al., 2014a), as well as reduced specificity of autobiographical retrieval (Dillon and Pizzagalli, 2018; Dalgleish et al., 2007; Williams et al., 2007). Other studies have demonstrated that those with greater symptoms of anxiety exhibit impaired memory of negative stimuli (Tofalini et al., 2015; Inaba and Ohira, 2009) suggesting a cognitive affective bias that leads to overgeneralization of negative emotional memories (Leal and Yassa, 2018; Kheirbek et al., 2012; Balderston et al., 2017).

We have previously shown that individuals with more depressive symptoms show augmented memory discrimination for negative items (Leal et al., 2014a) and exhibit unique neurobiological signatures which include reduced hippocampal dentate gyrus/CA3 activity and increased amygdala activity during the correct discrimination of highly similar negative (but not neutral) items (Leal et al., 2014b). These results were consistent with other literature

on depression that find evidence of a negativity bias (for review see Haas and Canli, 2008; Hasler et al., 2004) and functional and structural differences in the amygdala (MacMillan et al., 2003; Sheline et al., 2001; Whalen et al., 2002) and the hippocampus (Stockmeier et al., 2004).

Given prior work, there is uncertainty as to how greater depressive symptoms can be associated with augmented negative memory performance while greater anxiety symptoms can be associated with impaired negative episodic memory performance given that these two constructs are often comorbid and present together. Prior work, however, did not take into consideration the comorbidity of depression and anxiety, and the presence of subthreshold anxiety symptoms. In this investigation, we used exploratory factor analysis, applied to the BDI and BAI to uncover latent constructs of anxiety and depression in a clinically assessed cohort. We then tested the association of individual factors with memory performance, focusing on two primary outcome measures including target recognition (TR) assessing gist or generalized knowledge and Lure Discrimination Index (LDI) assessing detail knowledge or high precision memories (Norman, 2010; Yonelinas et al., 2010; Leal et al., 2014a).

2. Methods

2.1. Participants

Participants were recruited in collaboration with the department of Psychiatry and Human Behavior at the UC Irvine Medical Center and compensated for their participation. Participants were of 79 young adults (58 female) aged 18 to 41 years-old. This sample was comprised of 22 healthy participants (14 female) and 57 participants with a clinical diagnosis (44 females; see Clinical Diagnosis section). All procedures were in accordance with protocols approved by the UC Irvine Institutional Review Board. All participants provided informed consent prior to participation in the study. Participants were pre-screened before enrollment in the study for the presence of active depressive symptoms. These participants filled out a version of the Beck Depression Inventory without question nine (related to suicidality) online as part of their eligibility pre-screening. A score of 16 or higher on the pre-screening BDI-II determined eligibility to enroll in the study group. A matched sample of healthy control participants were recruited and had to satisfy the inclusion criterion of a BDI score less than 12. Once enrolled in the main study, the full version of the Beck Depression Inventory (BDI-II) was administered in person during the first study visit along with the Beck Anxiety Inventory (BAI) and other mood and sleep questionnaires. This in person administration of the BDI-II was used in all of our calculations. Table 1 describes the sample demographics.

2.2. Structured clinical interview (SCID)

As part of the study procedure, all participants underwent a two-hour semi-structured clinical interview with a clinician (I.Y.C. or R. M. B.) as outlined by the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV). The SCID-5-RV is a semi structured interview guide for making the major Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnoses. After completing this clinical interview, the clinician completed an accompanying summary sheet to determine the participant's current and past

diagnoses. The summary sheet additionally allowed the clinician to indicate whether a participant met subthreshold criteria for any relevant diagnosis. In the DSM-5 there are often multiple criteria or symptom types that need to be met in order to meet the full diagnosis requirements. A sub-threshold diagnosis was marked if the participant met a number of the criteria outlined in the DSM-5 corresponding to a particular disorder but did not meet ALL of the criteria necessary for a full diagnosis under the DSM-5.

2.3. Clinical diagnosis

In order to incorporate the SCID diagnoses into the analysis, we used a tag system to simplify the variety of clinical diagnoses. Healthy (H) participants ($N = 22$) underwent the full SCID Interview and had no history of psychopathology or clinical diagnosis. Participants whose SCID diagnosis revealed a past, subthreshold or active unipolar depression were designated with a Depression (D) tag ($N = 29$). For this sample, every participant with the "D" tag had a history of Major Depressive Disorder, a small subset ($n = 3$) also had a comorbid Persistent Depressive Disorder diagnosis and one ($n = 1$) had a comorbid Premenstrual Dysphoric Disorder diagnosis. The tag $D + A$ (depression comorbid with anxiety; $N = 18$) was given to participants who were eligible for the "D" tag but also had clinically identifiable anxiety. We considered this to be any participant with an active threshold or subthreshold anxiety disorder or obsessive-compulsive disorder. In this population, this included Generalized Anxiety Disorder ($n = 6$), Agoraphobia ($n = 2$), Panic Disorder ($n = 5$), Social Anxiety Disorder ($n = 4$), Specific Phobia ($n = 7$), Obsessive-compulsive Disorder ($n = 7$). Obsessive-compulsive disorder (included in the obsessive-compulsive and related disorders), was previously considered an anxiety disorder in the DSM-4. While it now has its own chapter in the DSM-5, these disorders are still considered to be closely related. Remaining participants receiving a SCID diagnosis that did not include an element of unipolar depression were tagged with the "Other" designation ("O"; $N = 10$). These participants were included despite not having a depression diagnosis to increase sample size and examine the effect of symptom severity even in the absence of a depression diagnosis. A full description of all clinically relevant diagnoses derived from the SCID for each participant is described in Supplementary Table 1.

2.4. Emotional pattern separation (EmoPS) task

The Emotional Pattern Separation task was administered on a sub-sample of 73 participants. The task consisted of a study phase and a test phase. The study phase consisted of 149 trials. In each trial a randomized series of emotional and non-emotional scene images were presented at the center of the screen with a black background for 2500 ms each, separated by an inter-stimulus interval of 500 ms (fixation cross) (Fig. 1a). Participants were asked to identify the valence associated with each image (Negative, Neutral, Positive). The subsequent test phase consisted of 291 trials. During these trials participants viewed stimuli which were either (1) seen once before during the study phase (targets), (2) stimuli that were similar to ones seen in the study phase but not identical (lures), and (3) novel images never seen before (foils). Targets, lures, and foils were evenly distributed across the three emotional valences. Participants were asked to indicate via button press whether they believed the items were "Old" or "New". They were explicitly told that "Old" images had to be the exact same image they had seen in the previous encoding phase. Images

were characterized *a priori* for emotional valence (negative, neutral, positive), arousal (very calming to very exciting), and similarity (median split of similarity ratings into "high" and "low") (Leal et al., 2014a, 2014b).

Behavioral performance on the task was quantified using two key measures. First we quantified target recognition (TR) using d-prime, a standard discriminability index that quantifies target hit rate, while correcting for false alarms. It is operationalized as z(Target Hit rate) – z (Foil False Alarm rate). Additionally, we calculated a lure discrimination index (LDI) operationalized as p("New"|Lure) – p("New"|Target) which quantifies lure discriminability and corrects for a "New" response bias. Extreme hit and false alarms rates (for lures and foils) were corrected following the methods of Stanislaw and Todorov (1999).

Two versions of the task were administered due to change in software. Twenty-six participants completed the task administered via version one conducted on MATLAB (RRID:nlx_153890, Version R2010a, Natick, MA) software with PsychToolbox version 3.0. Forty-seven participants completed the task using version 2 conducted using PsychoPy. Task versions varied slightly in the size of the images used. In addition, the PsychToolbox version of the task was conducted with visual confirmation of the study responses. Additional analyses are included in Supplementary Fig. 1 to rule out any behavioral differences between task versions.

2.5. Statistical analysis

Exploratory Factor analysis were conducted on questions derived from the BDI-II and BAI using the 'Psych' toolbox available in R (https://rstudio.com). Verimax rotated principal components were used. Similar to Lee et al. (2018) we allocated items to a specific factor using the criterion of a loading of more than 0.30 on the corresponding factor and items were excluded if the difference of the factor loading was less than 0.10 for a particular item. We tested if continuous measures of anxiety (BAI), and depression (BDI-II), as well as Factors 1 through 5, were normally distributed using the Shapiro-Wilk normality test from the 'stats' package in R (Royston, 1995). The results confirmed no continuous measure of depression, anxiety, nor the factor scores were normally distributed. As such, Spearman's correlation coefficients (r_s) were calculated using R to evaluate the relationships between continuous measures of anxiety and depression and memory performance. Multiple linear regression analyses were conducted in R to account for confounding variables including age and sex in the relation between anxiety and depression and memory performance. Standardized beta coefficients are reported in-text and were calculated using the 'lm.beta' package in R. Two-way ANOVA was used to determine differences in task performance across versions and task performance as a function of clinical diagnosis. To ensure Multiple comparisons were corrected for within-family (emotional valence) bivariate analyses of the factor relation to emotional pattern separation behavior using the Benjamini-Hochberg procedure implemented in R (Benjamini and Hochberg, 1995). Bootstrap analysis were conducted using the Boot package available in R-Studio with 1000 repetitions and 95% confidence intervals are reported.

3. Results

3.1. Overall EmoPS performance does not vary by clinical diagnosis

We first asked if behavioral performance differed as a function of clinical diagnosis. There was no significant interaction between diagnosis and emotional valence for LDI performance ($F_{4,189} = 0.50$, $P = 0.74$; Fig. 1b) or TR performance ($F_{4,189} = 0.89$, $P = 0.47$; Fig. 1c). Across the whole sample, LDI performance was significantly different ($F_{2,216} = 5.40$, $P = 0.005$; Supplementary Fig. 2a) with participants performing worse for positive stimuli compared to neutral (*adjusted* $P = 0.0034$). We found no behavioral difference in TR across emotional valence for all participants ($F_{2,216} = 1.50$, $P = 0.22$; Supplementary Fig. 2b). For all subsequent analyses, we chose to focus on the negative and neutral items and did not consider the positive items as they were not well-matched to the negative for arousal ratings, however, results with positive stimuli are represented for reference in Supplementary Fig. 5.

3.2. Anxiety symptom severity is associated with impaired memory performance for negative items

We first explored the degree to which anxious and depressive symptoms, across all participants, were related to one another using the cumulative inventory totals from the BAI and BDI-II inventories. We found a strong association between scores on BDI-II and BAI across all participants ($r_s = 0.80$, $P < 0.0001$; Fig. 2). We then asked if depression and anxiety scales were associated with LDI and TR for negative and neutral items. We found that greater depressive symptoms were not associated with LDI for negative ($r_s = -0.14$, $P = 0.22$; Supplementary Fig. 3a) or neutral ($r_s = -0.055$, $P = 0.65$; Supplementary Fig. 3b) items. Similarly, total anxiety symptoms were not associated with LDI for negative ($r_s = -0.19$, $P = 0.10$; Supplementary Fig. 3c) or neutral ($r_s = -0.10$, $P = 0.39$; Supplementary Fig. 3c) items.

We found that more depressive symptoms ($r_s = -0.25$, $P = 0.032$; Fig. 3a) and more anxiety symptoms ($r_s = -0.31$, $P = 0.0081$; Fig. 3c) were associated with lower TR for negative items. The relationship between depressive symptoms and lower TR for negative items did not remain significant after accounting for age and sex ($\beta = -0.22$, $P = 0.11$; Supplementary Table 2). However, the relationship between anxiety symptoms and lower TR for negative stimuli did remain significant after accounting for age and sex ($\beta = -0.35$, $P = 0.0088$; Supplementary Table 3). We then tested if depression or anxiety was related to TR for neutral items. Neither depressive symptoms ($r_s = -0.087$, $P = 0.51$; Fig. 3b) nor anxiety symptoms ($r_s = -0.11$, $P = 0.36$; Fig. 3d) were associated with TR for neutral items. Interestingly, the relationship between symptoms of anxiety and lower TR for negative stimuli was driven by targets hit rate for negative stimuli ($r_s = -0.37$, $P = 0.0013$; Supplementary Fig. 4a) and not false alarm rate ($r_s = 0.020$, $P = 0.87$; Supplementary Fig. 4b).

3.3. Exploratory factor analysis and relation to clinical diagnoses

As a result of the strong association between depressive and anxious symptoms we sought to determine if sub-clusters of symptoms were more strongly associated with different facets of emotional memory performance. Utilizing the full sample (N=79) we found that the

Kaiser-Meyer-Olkin measure (0.85) and Barrett's test of sphericity (approximate Chi-square = 876.55, 661 degrees of freedom, $P < 0.0001$) provided evidence that the use of the exploratory factor approach was appropriate for these data and that 5 factors were sufficient. Factor analysis revealed that the following 5 factors explained approximately (59%) of the variance. We note that some factors include symptoms that may typically be associated with other clinical constructs. **Factor 1 (Negative Affect)** is composed of 6 items from the BDI-II which include "Pessimism", "Past Failure", "Self-dislike", "Self-criticalness", "Suicidal thoughts or wishes", "Worthlessness". **Factor 2** (**Anhedonia-like**) is composed of 8 items from the BDI-II which include "Loss of pleasure", "Punishment feelings", "Loss of energy", "Irritability", "Crying", "Loss of interest", "Concentration difficulty", "Tiredness or fatigue". **Factor 3** (**Somatic Anxiety**) is composed of 7 items from the BAI including "Feeling hot", "Dizzy or lightheaded", "Feeling of choking", "Faint lightheaded", "Face flushed", "Hot/cold sweats", "Difficulty breathing". **Factor 4** (**Cognitive Anxiety**) is composed of 5 items on the BAI and one item on the BDI-II which include "Unable to relax", "Fear of worst happening", "Unsteady", "Nervous", "Fear of losing control", "Changes in sleeping pattern". **Factor 5 (Somatic Anxiety)** is composed of 3 items on the BAI which include "Wobbliness in legs", "Hands trembling", "Shaky unsteady". The factor loadings are summarized in Table 2. In order to quantify the external validity of the item factor identities calculated in our sample, we quantified a normalized mutual information (NMI) score representing the degree of consistency of our results with previously published reports. In direct comparison to item factor identities of a large ($n = 406$) clinical population, we report a NMI of 0.67 indicating moderate overlap within the clustering of BAI and BDI-II questions across samples (Lee et al., 2018). Factor scores were quantified by summing respective items within each factor.

We then asked if factors from our exploratory factor analysis were able to distinguish among different clinical diagnoses (H, D, D+A, and A). We found a significant main effect of factor ($F_{4,330} = 56.35$, $P < 0.0001$), clinical diagnosis ($F_{2,330} = 147.6$, $P < 0.0001$), as well as a significant factor x clinical diagnosis interaction ($F_{8,330} = 8.41$, $P < 0.0001$). Post-hoc comparisons revealed that Factors 1 (Negative Affect), 2 (Anhedonia), 3 (Somatic Anxiety), and 4 (Cognitive Anxiety) were able to distinguish the H and D groups as well as H and D+A groups (Fig. 4). No factor was able to distinguish the D and D+A group. Factor 5 (composed from 3 questions from the BAI) was not sufficient to dissociate the H from clinical groups (D, D+A). Due to this analysis, we decided not to include Factor 5 in subsequent analyses.

3.4. Factor relation to EmoPS performance

We then sought to determine if latent factors of anxiety and depression were associated with impaired EmoPS performance. In separate analyses, we correlated each factor with EmoPS performance for negative and neutral stimuli correcting for multiple comparisons within family using the Benjamini-Hochberg procedure.

First, we found that greater total scores for Somatic Anxiety ($r_s = -0.24$, *unadjusted* $P = 0.038$; Fig. 5c) and Cognitive Anxiety ($r_s = -0.27$, *unadjusted* $P = 0.019$; Fig. 5d) were associated with impaired negative TR. The association between Somatic Anxiety and

negative TR performance was significant after accounting for age and sex (β = −0.27, P = 0.036; Supplementary Table 4). Similarly, the association between Cognitive Anxiety and negative TR performance was significant after accounting for age and sex (β = −0.33, P = 0.020; Supplementary Table 5). However, after correcting for multiple comparisons, neither Somatic Anxiety (*adjusted P* = 0.077) nor Cognitive Anxiety (*adjusted P = 0.077*) were significantly associated with negative TR performance. In addition, we note that greater measures of Negative Affect (r_s = −0.20, *unadjusted P* = 0.082; Fig. 5a) and Anhedonia-Like factors (r_s = −0.21, *unadjusted P* = 0.074; Fig. 5b) were marginally associated with impaired negative TR.

As a result of the non-normal distribution of Somatic Anxiety scores and Cognitive Anxiety scores and to ensure these effects were not driven by individual points having a large effect we conducted bootstrap analysis with 1000 simulations. The 95% confidence interval for the Spearman's correlation coefficient bootstrap effect for the relationship between Somatic Anxiety and negative TR ranged from −0.45 to −0.030 (SE = 0.11). The 95% confidence interval for the Spearman's correlation coefficient bootstrap effect for the relationship between Cognitive and negative TR ranged from −0.48 to −0.056 (SE = 0.11). No Factor was associated with negative or neutral LDI after correcting for multiple comparisons (Supplementary Fig. 6).

4. Discussion

There are three key findings in this study. First, our exploratory factor analysis provides evidence that symptoms of anxiety and depression may be broken into constituent components namely Negative Affect, Anhedonia-Like symptoms, Somatic, and Cognitive Anxiety. Second, we find that factors from our exploratory factor analysis are able to dissociate clinical diagnoses from healthy controls, however, diagnoses of depression and depression comorbid with anxiety are not differentiable in this small sample using these latent factors. Third, we find that greater symptoms of anxiety are associated with impaired recognition for negative items but not neutral items. The contributions of anxiety and depression to emotional episodic memory disruption have long been a target of investigation in humans, however, most work has focused on sub-clinical symptoms and the comorbidity of anxiety and depression symptoms are often left untested (Dillon and Pizzagalli, 2018).

A general framework for the episodic memory dysfunction in depression suggests a negativity memory bias or augmented memory for negative material (Dillon and Pizzagalli, 2018; Leal et al., 2014a, 2014b; Burt et al., 1995) whilst also displaying impaired recollection or "overgeneralized" autobiographical retrieval (Dalgleish et al., 2007; Williams et al., 2007). These performance differences are often coupled with volumetric and functional differences in the hippocampus (Stockmeier et al., 2004) as well as amygdala (MacMillan et al., 2003; Sheline et al., 2001; Whalen et al., 2002). We have previously shown in an undiagnosed sample that individuals reporting with greater depressive symptoms show augmented discrimination for negative items (Leal et al., 2014a). We have also shown that higher depressive symptoms were associated with augmented amygdala activity and attenuated DG/CA3 activity during correct discrimination of negative items compared to neutral items (Leal et al., 2014b).

In this investigation, we provide evidence that symptoms of anxiety are associated with impaired recognition for negative stimuli and not neutral stimuli. This relationship also persists after accounting for age and sex. In addition, across the whole sample, continuous measures of depression and anxiety were highly correlated, which suggests that multiple regression on its own may not be the most suitable method for capturing the effects of depressive symptoms when highly comorbid with anxiety.

To address this concern, we implemented the use of exploratory factor analysis to uncover latent constructs of anxiety and depression and to determine whether symptoms could be meaningfully clustered together. We identified 5 factors, two composed of questions derived from the BDI-II generally reflecting Negative Affect (Factor 1) and Anhedonia-like symptoms (Factor 2) and 3 composed of questions derived largely from the BAI (Factor 3/5: Somatic Anxiety/hyper-arousal; Factor 4: Cognitive Anxiety). While we note we were able to derive factors that included largely separable factors of depression and anxiety, we note that factor 4 (Cognitive Anxiety) is composed of 5 items from the BAI and 1 item (changes in sleeping pattern) from the BDI-II. This approach has been previously used to test the hypothesis that coexisting symptoms of anxiety and depression (derived from the BAI and BDI-II) can be differentiated into a tripartite model including general negative affectivity (NA), anxiety (physiological hyper-arousal), and depression (low positive affectivity) (Lee et al., 2018; Clark and Watson, 1991). In this sample, we demonstrate considerable overlap in the clustering of item-factor identities compared to previously published reports (Lee et al., 2018) and note that questions related to BDI and BAI largely clustered onto separate factors.

While we found that our item-factor identities were comparable with other investigations and were able to dissociate healthy participants from clinical groups (D, D+A), we did not find evidence that our factors were able to dissociate individuals with a depression diagnosis alone from those with depression and a comorbid anxiety disorder indicating similar degree of negative affect, anhedonia-like symptoms, cognitive and somatic anxiety across clinical groups. Thus, it is possible that while similar factor constructs have been successful at separating clinical depression and anxiety diagnoses (Lee et al., 2018), the factor identity approach in this investigation is not capable of dissociating depression and depression with comorbid anxiety symptoms. One possibility is the prevalence of subsyndromal or subthreshold anxiety in depression which may make the distinction based on factors and symptoms more difficult.

Regardless of this distinction, we used these factors to determine if specific aspects of depression or anxiety were associated with impaired recognition for negative stimuli. We found that both constructs of anxiety, including somatic anxiety/hyperarousal as well as cognitive anxiety, were associated with impaired recognition of negative stimuli but not neutral stimuli.

The hypothesis that anxiety-like symptoms are related to impaired episodic memory dysfunction has been tested before. Notably, experimentally induced symptoms of anxiety in both humans and animal models suggest an effect of overgeneralization and impaired memory performance. For instance, animals who have undergone fear conditioning freeze when exposed to a similar but not identical operant chamber (Kheirbek et al., 2012). In

humans, experimentally induced symptoms of somatic anxiety (via shock expectancy) were associated with impaired performance on a pattern separation task (Balderston et al., 2017). Others have suggested that anxiety leads to overgeneralization through impairments in pattern-separation mediated mechanisms (Sahay et al., 2011; Leal et al., 2014a, 2014b). However, here we show for the first time that clinical levels of cognitive and somatic anxiety, distinguished from depressive symptoms, are related to impaired recognition memory for negative stimuli in a clinical sample.

In a recent review, Dillon and Pizzagalli (2018) suggest that while depressive symptoms have been linked with augmented pattern separation for negative stimuli, it is possible that impaired pattern separation may be a feature in depressed individuals who also express comorbid anxiety. The current study suggests that anxiety is associated with worse recognition rather than worse discrimination. This performance pattern is consistent with the notion that anxiety impairs episodic memory function for negative stimuli (Tofalini et al., 2015; Inaba and Ohira, 2009).

Certainly, the interplay between depression and anxiety may be even more complex and includes factors such as the duration of expression of each type of symptom or the age of onset of symptoms. For example, we have previously shown that post-encoding stress in healthy individuals is able to enhance the discrimination of negative stimuli but not neutral stimuli (Cunningham et al., 2018). Similarly, also in healthy adults, an exaggerated noradrenergic response elicited by viewing threatening images yielded augmented memory performance for negative but not neutral items (Segal and Cahill, 2009). Perhaps memory performance is a function of severity of psychiatric morbidity. In this case, we may observe augmented discrimination of negative events early in subclinical levels of depression, however as depression progresses, stress levels become more elevated and the storage of negative experiences accumulates, subsequently leading to impaired discrimination or recognition as the disease progresses and the comorbidity with anxiety becomes more established, similar to the theory proposed by Dillon and Pizzagalli (2018).

It is hypothesized that the EmoPS task used in this investigation engages a neuronal computation known as pattern separation which is thought to be heavily reliant on the dentate gyrus (DG) and the CA3 regions of the hippocampus (Yassa and Stark, 2011). The CA3 is thought to maintain a balance between storing new experiences using pattern separation and re-instantiating previously stored experiences using “pattern completion”. The latter function in particular is thought to be reliant on the recurrent collateral network of the CA3 (Yassa and Stark, 2011; Rolls, 2007). One possibility is that the relation between greater anxiety and impaired recognition for negative stimuli may be attributed to impaired CA3 function. In animals, chronic stress is thought to induce preferential loss of CA3 apical dendrite length and branching as well as dendritic spine density (Sousa et al., 2000; Magariños and McEwen, 1995; Magariños et al., 1996; Vyas et al., 2002; Soetanto et al., 2010). Similar evidence has been found in *ex-vivo* samples in humans of those with clinical depression, namely decreased dendrite and spine densities in the CA3 region (Soetanto et al., 2010), although we note that these histological effects are not entirely specific to the CA3 region with other studies finding differences in the amygdala (Vyas et al., 2003), prefrontal cortex (Radley et al., 2004) as well as other regions. The stress-induced loss of

CA3 connectivity in particular could impair its ability to process input from the entorhinal cortex thereby leading to an impairment in pattern completion or recognition. This could potentially explain the failure of recognition we observe in individuals with high levels of anxiety. Future research could test the hypothesis that CA3 function may be a mechanistic contributor to the recognition failure in anxiety.

One potential limitation of this study is the use of a clinical sample with mixed pathology that includes varying levels of depression and anxiety. While this may be more representative of the population, it does make interpretations more difficult with respect to depression alone, anxiety alone, or comorbid depression and anxiety given the smaller sample sizes. Additionally, we note that while our sample did contain a group of subjects with clinical history of depression and history of clinically diagnosed co-morbid depression and anxiety, continuous measures of symptoms were not sufficient to dissociate the two. Additionally, we note that we did not explicitly test the relationship between symptom severity and memory discrimination or recognition of positive stimuli. This was intentionally the case for two reasons. First, our prior work focused on the differences between negative and neutral stimuli specifically (Leal et al., 2014a, 2014b). Second the positive stimuli were not matched for arousal ratings compared to the negative images and thus would be difficult to compare. Future work could perhaps examine a different kind of positive stimulus such as stimuli that elicit stronger hedonic value.

In conclusion, we provide evidence that symptoms of anxiety, controlling for co-morbid depression, are associated with impaired recognition for negative stimuli. Our exploratory factor analysis revealed that this relationship is present in both somatic and cognitive symptoms of anxiety. These results are consistent with a dimensional understanding of psychiatric pathology and pave the path to more mechanistic studies to understand the neural mechanisms of memory impairment in anxiety and depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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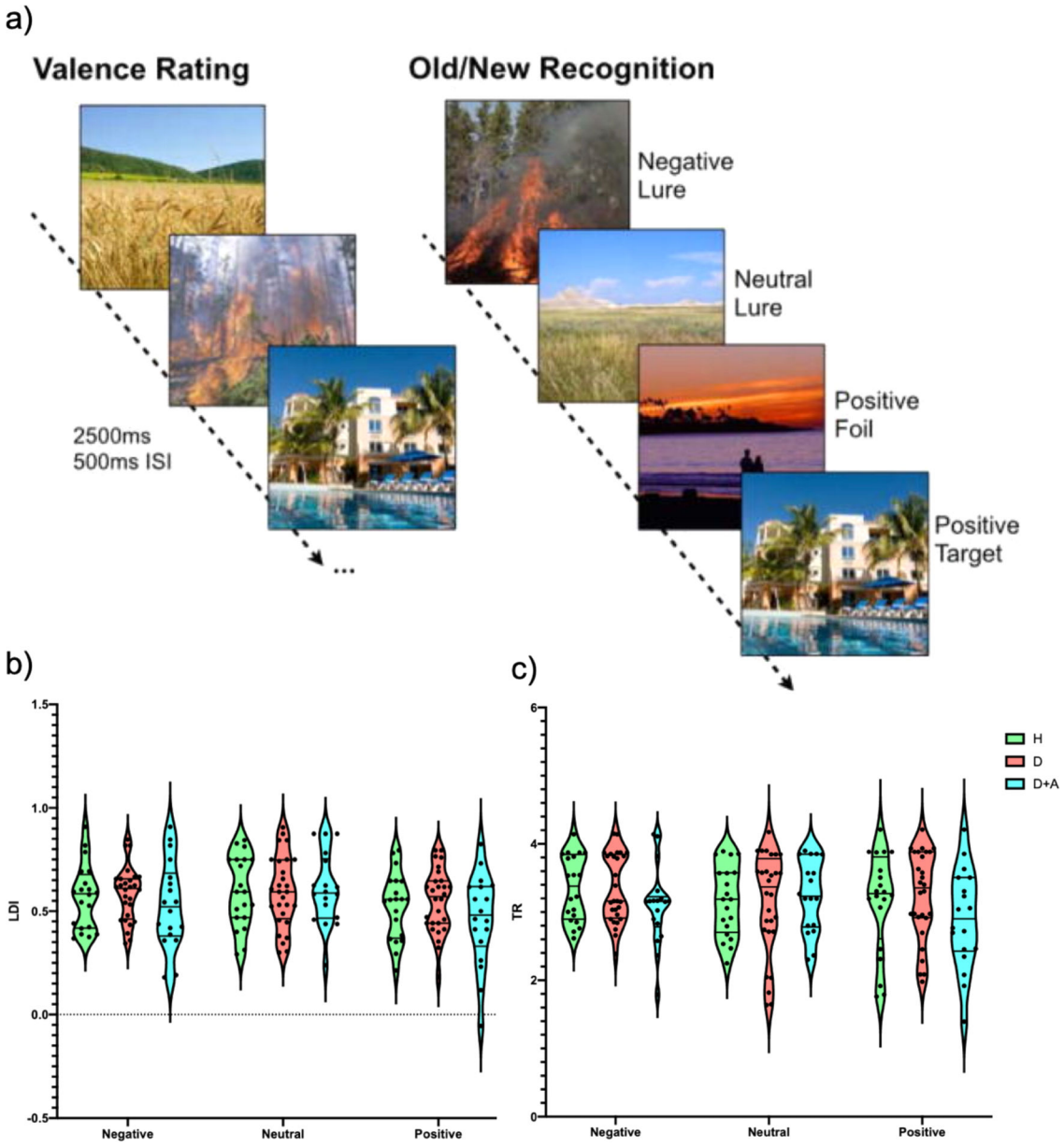

Fig. 1.

(a) The emotional pattern separation paradigm. During study participants are asked to rate the valence of the images either positive, negative, or neutral. During test, participants are asked to make “old” or “new” judgements. Images are varied from study such that some images are slightly altered ‘lures’, other images are novel ‘foils’, or repeated (targets). Images are varied as a function of emotional valence (positive, negative, neutral) as described in our previous work (Leal et al., 2014a, 2014b). (b, c) No difference between clinically assessed groups on emotional pattern separation performance for (b) lure discrimination and (c) target recognition (TR).

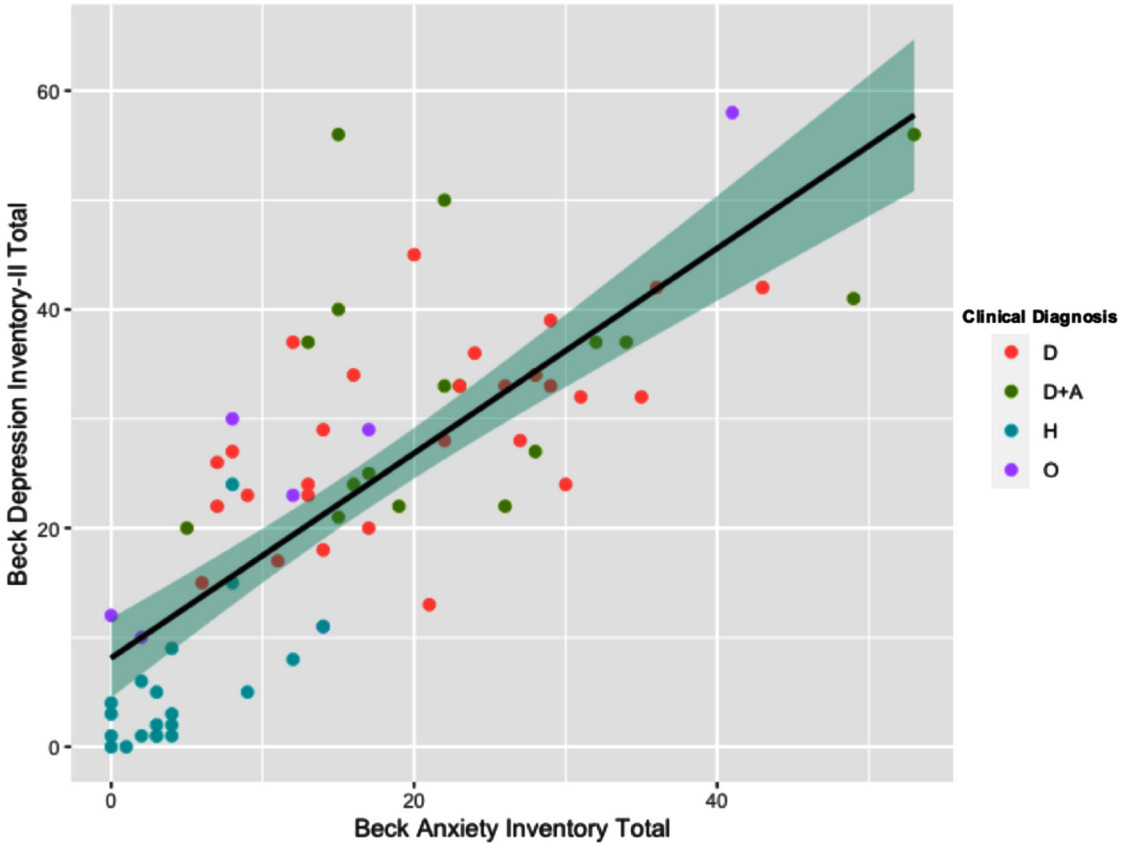

Fig. 2.
Clinical diagnosis plotted as a function of BDI-II inventory and BAI inventory total scores.

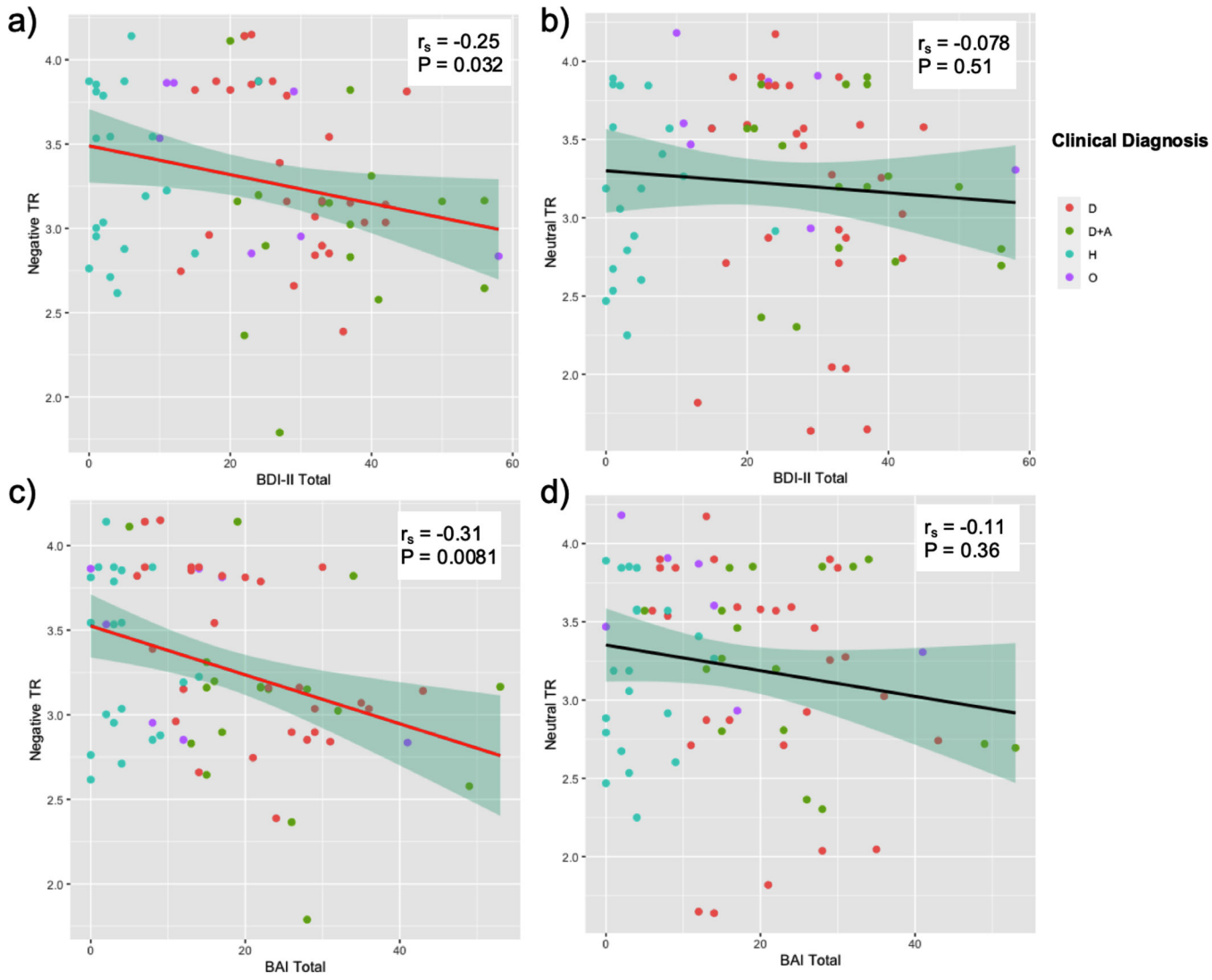

Fig. 3.

Association between BDI-II (a, b) and BAI (c, d) inventory totals and target recognition (TR) for negative (a, c) and neutral (b, d) items.

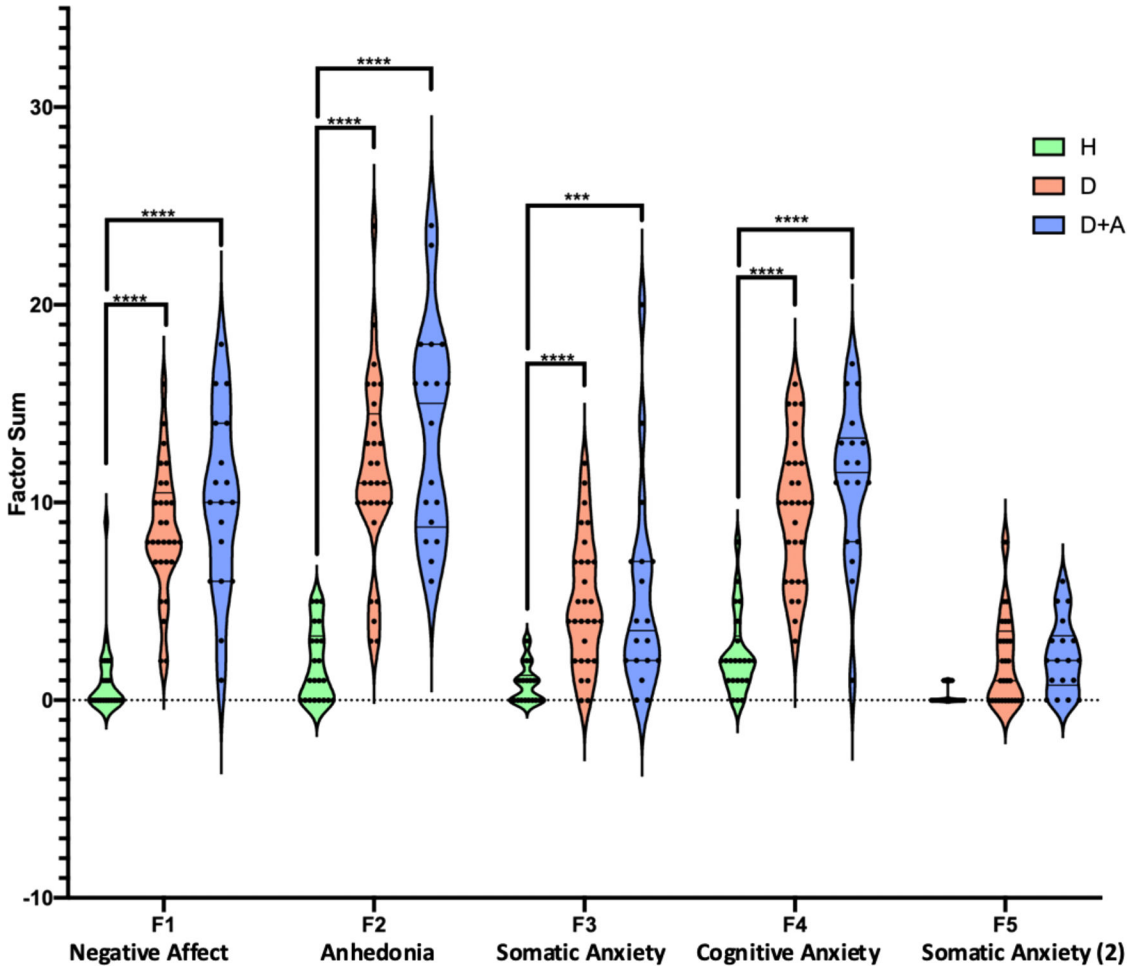

Fig. 4.

Factor analytics dissociate healthy from psychiatric diagnoses as well as those with anxiety from those with comorbid depression. ****Indicates $P < 0.0001$, ***Indicates $P < 0.001$, **Indicates $P < 0.01$, *Indicates $P < 0.05$.

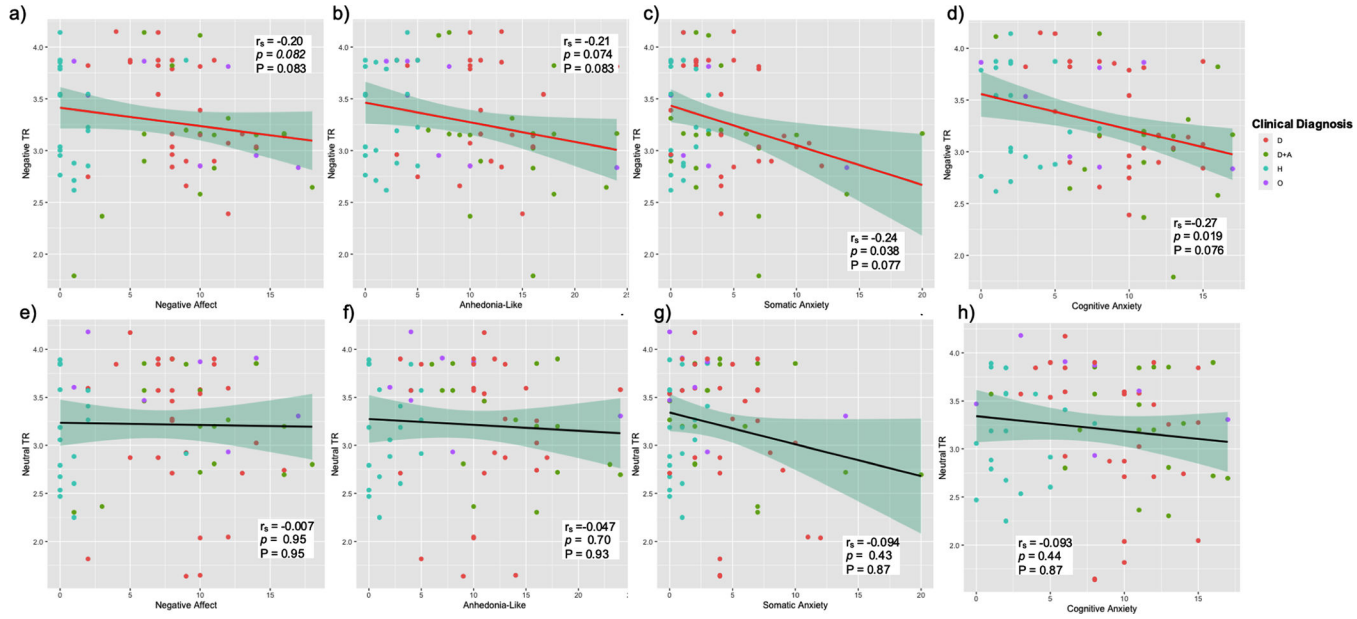

Fig. 5.

(a–d) Show the relationship between Factors 1–4 and Target Recognition (TR) for negative items. (e–h) Show the relationship between Factors 1–4 and TR for neutral items. *p* indicates p-value prior to correcting for multiple comparisons. P indicates p-value after correcting for multiple comparisons.

Table 1

Participant demographics ($N = 79$). The subgroup of participants able to complete the emotional pattern separation task is denoted by n.

	Full Sample*N* = 79*n* = 73	**H(Healthy)*N* = 22*n* = 20**	**D(Depression)*N* = 29*n* = 28**	**D + *A*(Depression + Anxiety)*N* = 18*n* = 18**	**O(Other)*N* = 10*n* = 7**
Age	23.21 ± 5.71 (1 missing)	26.38 ± 6.78 (1 missing)	22.61 ± 5.18	20.91 ± 3.76	22.46 ± 5.59
Sex	58 Female	14 Female	23 Females	15 Females	6 Females
	21 Male	8 Male	6 Males	3 Males	4 Males
Trails A	37.83 ± 22.20	36.27 ± 25.00	37 ± 22.83	38.83 ± 19.74	41.88 ± 20.67
Trails B	39.31 ± 22.38	39.50 ± 24.43	36.55 ± 21.27	43.17 ± 18.66	39.91 ± 28.77
MMSE	28.87 ± 1.19	28.73 ± 1.16	28.97 ± 1.09	28.78 ± 1.17	29.10 ± 1.66
BDI-II	23.23 ± 15.05	4.86 ± 5.79	29.1 ± 8.33	34.17 ± 11.43	26.90 ± 15.23
BAI	16.67 ± 13.12	3.96 ± 3.89	20.9 ± 10.20	24.00 ± 12.22	19.20 ± 16.86
RAVLT Immediate Recall	12.63 ± 2.35	12.32 ± 2.21	13.69 ± 1.47	11.33 ± 2.99	12.6 ± 2.41
RAVLT Delayed Recall	12.58 ± 2.69	12.5 ± 2.99	13.45 ± 1.74	11.50 ± 2.75	12.2 ± 3.65
Digit Span Forward	11.04 ± 2.46	10.73 ± 2.43	11.62 ± 2.58	10.22 ± 2.32	11.50 ± 2.17
Digit Span Backward	7.70 ± 2.51	7.59 ± 2.42	8.41 ± 2.63	6.78 ± 2.39	7.5 ± 2.27

Table 2

Exploratory factor analysis on 42 items from the BDI-II and BAI.

Inventory Identity	Items	Factor1	Factor2	Factor3	Factor4	Factor5	Uniqueness
D	**Pessimism**	**0.77712804**	0.26485042	0.24539489	0.13132086	0.18068717	0.2158115
D	**Past.Failure**	**0.72389638**	0.28607047	0.15753857	0.21679833	0.04211347	0.3205434
D	**Self.Dislike**	**0.82989106**	0.17227467	0.21814166	0.18228313	0.16831923	0.1724534
D	**Self.Criticalness.**	**0.64141483**	0.41729106	0.04350299	0.27373267	0.1111219	0.325283
D	**Suicidal.Thoughts.or.Wishes**	**0.50809463**	0.25129772	0.19716152	0.17658526	−0.0708959	0.6036264
D	**Worthlessness**	**0.76938677**	0.27262725	0.23716295	0.14848121	0.19582645	0.2170714
D	**Loss.of.Pleasure**	0.39160704	**0.74175296**	0.10688447	0.25363353	0.25373843	0.1563097
D	**Punishment.Feelings.**	0.15389157	**0.51866528**	0.41344227	0.38453728	0.07981183	0.3821329
D	**Loss.of.Energy**	0.30080003	**0.66582562**	0.34871762	0.12285838	0.05939576	0.3259721
D	**Irritability**	0.19712994	**0.69748212**	0.31468192	0.19986512	0.15477788	0.3117314
D	**Crying**	0.3797373	**0.51038543**	0.33966752	0.23245771	0.08895584	0.4179916
D	**Loss.of.Interest**	0.498363	**0.67982493**	0.11051959	0.17688203	0.15742587	0.2211836
D	**Concentration.Difficulty.**	0.34972679	**0.61252432**	0.37267319	0.24507253	0.14257013	0.2832343
D	**Tiredness.or.Fatigure**	0.43846048	**0.54759452**	0.19561457	0.25802558	0.11055606	0.3908366
A	**Feeling.hot**	0.06833009	0.28447635	**0.54870155**	0.15790325	0.09230075	0.5798775
A	**Dizzy.or.lightheaded**	0.17921664	0.29255929	**0.45197241**	0.20154835	0.31058593	0.5409226
A	**Feeling.of.choking**	0.27931474	0.04698573	**0.61724742**	0.12018748	0.24938522	0.4621248
A	**Faint...lightheaded**	0.10020839	0.16722285	**0.58430755**	0.1223727	0.20330428	0.5642958
A	**Face.flushed**	0.07680063	0.29889648	**0.52385807**	0.33669589	0.01042321	0.51686
A	**Hot.cold.sweats**	0.16979326	0.17184826	**0.60430486**	0.1738053	0.08897877	0.5383305
A	**Difficulty.in.breathing**	0.13198328	0.17879972	**0.5613848**	0.31377414	0.31635837	0.4369234
A	**Unable.to.relax**	0.36887081	0.42389236	0.1115699	**0.61417268**	0.27255906	0.2203042
A	**Fear.of.worst.happening**	0.35786713	0.1422663	0.27689994	**0.75375787**	0.09252536	0.198305
A	**Unsteady**	0.12037013	0.23477716	0.37798279	**0.5345359**	0.40700198	0.336145
A	**Nervous**	0.36023396	0.41327091	0.26772248	**0.60153356**	0.19531759	0.227773
A	**Fear.of.losing.control**	0.26797756	0.12804534	0.33455202	**0.47816862**	0.14844334	0.5491919
D	**Changes.in.Sleeping.Pattern**	0.1413271	0.33987445	0.30367662	**0.45596967**	0.04537547	0.5623314
A	**Wobbliness.in.legs**	0.14593026	0.11333084	0.17566114	0.04102021	**0.68420866**	0.4651598

Inventory Identity	Items	Factor1	Factor2	Factor3	Factor4	Factor5	Uniqueness
A	**Hands.trembling**	0.19485941	0.10195464	0.39229553	0.21331583	**0.67657523**	0.2944797
A	**Shaky...unsteady**	0.19484544	0.16675031	0.33721594	0.41908604	**0.59418618**	0.2918279
A	**Terrified.or.afraid**	0.30510065	0.0837911	0.51328803	0.55796227	0.13328116	0.3073458
A	**Heart.pounding.racing**	0.1930554	0.27914337	0.38177393	0.4551212	0.34185197	0.4150663
A	**Fear.of.dying**	0.28820349	0.00985847	0.35279735	0.13337594	0.09094666	0.766345
A	**Scared**	0.23180329	0.13712659	0.56696583	0.52408894	0.19122457	0.2947798
A	**Indigestion**	0.21175663	0.30901897	0.38752316	0.03652352	0.0933679	0.6994472
D	**Indecisiveness**	0.46768346	0.4038309	0.29903708	0.32355287	0.18977075	0.3880737
D	**Changes.in.Appetite**	0.42127916	0.37261221	0.22696136	0.16330213	0.12367281	0.5902289
D	**Loss.of.Interest.in.Sex**	0.19114233	0.20696626	0.00992127	0.0111293	0.06832415	0.9158702
A	**Numbness.or.tingling**	−0.0629523	0.33115013	0.07546944	0.44474363	0.46753476	0.4642973
D	**Agitation**	0.34320327	0.40338675	0.12151812	0.29733925	0.09631173	0.6070728
D	**Guilty.Feelings**	0.37364309	0.38201784	0.26216535	0.34768085	0.21968799	0.4765714
D	**Sadness**	0.54186282	0.49744825	0.3999217	0.16048047	0.09065003	0.2650229
SS Loadings		6.166	5.806	5.322	4.671	2.717	
Proportion of Variance Explained		0.15	0.14	0.13	0.11	0.06	
Cumulative Variance Explained		0.15	0.29	0.41	0.52	0.59	