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Characterizing anxiety subtypes and the relationship to behavioral phenotyping in major depression: Results from the EMBARC study

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ABSTRACT

The current study aimed to characterize the multifaceted nature of anxiety in patients with major depression by evaluating distinct anxiety factors. We then related these derived anxiety factors to performance on a Flanker Task of cognitive control, in order to further validate these factors. Data were collected from 195 patients with nonpsychotic chronic or recurrent major depression or dysthymic disorder. At baseline, participants completed self-report measures of anxiety, depression, and other related symptoms (mania, suicidality) and clinicians administered a structured diagnostic interview and the Hamilton Rating Scale for Depression, including anxiety/somatization items. Four discrete factors (State Anxiety, Panic, Neuroticism/Worry, and Restlessness/Agitation) emerged, with high degrees of internal consistency. Discriminant and convergent validity analyses also yielded findings in the expected direction. Furthermore, the neuroticism/worry factor was associated with Flanker Task interference, such that individuals higher on neuroticism/worry responded more incorrectly (yet faster) to incongruent vs. congruent trials whereas individuals higher on the fear/panic factor responded more slowly, with no accuracy effect, to the Flanker Task stimuli. These results parse anxiety into four distinct factors that encompass physiological, psychological, and cognitive components of anxiety. While state anxiety, panic and neuroticism/worry are related to existing measures of anxiety, the Restlessness/Agitation factor appears to be a unique measure of general anxious arousal. Furthermore, two factors were independently validated through the Flanker Task. These results suggest that these anxiety domains have distinct behavioral profiles and could have differential responses to distinct treatments.

1. Introduction

The presence of anxious symptoms in depression significantly reduces the probability of remission when treated with antidepressant medications (Fava et al., 2008). Prior research evaluating anxious symptoms in depression has most often focused on particular aspects of anxiety that align with particular anxiety disorder diagnoses. For example, many questionnaires assess symptoms associated with a specific anxiety disorder, such as Generalized Anxiety (Spitzer et al., 2006), panic disorder (Shear et al., 1997), social anxiety (Iza et al., 2014), and PTSD (Gentes et al., 2014).

While diagnostic-oriented assessment may be helpful in tracking symptoms associated with specific DSM diagnoses and the impact of treatment, there has been a push to evaluate groups of symptoms in an alternative way that will more closely align with the underlying biology and behavior associated with psychopathology. The NIMH Research Domain Criteria (RDoC) initiative (Cuthbert, 2014; Insel et al., 2010) is one approach that suggests novel conceptualizations of

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psychopathology classification through five organizational domains.

Using diagnostic data, aspects of anxiety have been related to specific underlying biological systems that are distinct from depression (Kocovski et al., 2004). In fact, research has already identified the impact of comorbid anxiety on specific cognitive processes. For example, prior research has demonstrated how anxiety symptoms and disorders are associated with impaired cognition, attention, and behavioral task performance (Eysenck et al., 2007; Farber and Spence, 1956; Robinson et al., 2013). Using functional task-based brain imaging to probe both biological and cognitive abnormalities, Etkin and Schatzberg (2011) observed anxiety disorders to substantially modify emotional conflict regulation in the brain. While these data have elucidated the contribution of anxiety in patients with depression, further characterization of distinct factors within anxiety presentations has been lacking.

The goals of this study are (a) to use a wide selection of anxiety symptoms to determine if distinct anxiety factors can be defined and measured (b) to relate these factors to existing clinical assessments, and most importantly (c) to determine through validation, if they are relevant to performance on a behavioral task, the Flanker Task. To achieve these study aims, we utilized symptoms from six "anxiety" measures evaluating various anxiety facets (i.e., cognitive, physiological, and psychological components; anxiety disorder diagnoses). We used principal component analysis to define factors and report the relationship between these factors and other clinical measures for validation of the derived measures. We further validated these factors by associating them with performance on the Flanker Task, as prior research has revealed anxiety to negatively impact performance on this task (Chen et al., 2016; Huyser et al., 2011).

2. Methods

2.1. Study design and participants

Participants were recruited through advertising, flyers, and physician referrals for the multi-site Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study, a 16-week, placebo-controlled study to determine biological, physiological, cognitive, and genetic biomarkers of response to sertraline and bupropion (Trivedi et al., 2016). The EMBARC study recruited adult participants ages 18–65 from four sites around the United States and required participants to have recurrent or chronic single-episode major depressive disorder (MDD) or dysthymia, with the first onset before age 30. Participants were not included if they failed an antidepressant trial of sufficient dose and duration within the current episode. Key exclusion criteria included a history of inadequate response or poor tolerability to study medications; a history of psychotic or bipolar disorders; or substance dependence (except for nicotine) within the past six months or abuse within the past two months. The 16-week study consisted of two eight-week phases: at study entry, participants were randomized to receive either placebo or sertraline for eight weeks; then, at the 8th week mark, responders stayed on the initial treatment, non-responders to placebo were switched to sertraline, and non-responders to sertraline were switched to bupropion and followed for an additional eight weeks.

The study design was reviewed and approved by each site's IRB, and, before enrollment, all participants signed written informed consent after the procedures were fully explained. Participants completed a battery of self-report measures at baseline, with behavioral tasks, electroencephalographic (EEG), magnetic resonance imaging (MRI), and other assessments completed within the week prior to randomization. The data presented here include six self-report/clinician forms and behavioral data completed at the initial baseline session and/or at the first EEG session when no participant was currently receiving antidepressant medication. The data presented here encompasses 195 unmedicated participants.

2.2. Measures

Baseline clinician-administered measures included the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) – to determine current or lifetime history of depressive and anxiety diagnoses including Panic Disorder, Social Phobia, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Generalized Anxiety Disorder (current only), and Anxiety Disorder Not Otherwise Specified – alongside the anxious distress specifier for a major depressive episode. These items were treated as ordered, using the ratings of 1 (symptoms of the disorder were absent), 2 (sub-threshold symptoms present), and 3 (diagnostic threshold met). If there were no current diagnoses present, lifetime diagnoses were used, since, by definition, current disorders were also lifetime disorders. In addition to the six SCID anxiety disorders and the anxious distress specifier for an MDE, six items from the 17-item clinician-rated Hamilton Depression Rating Scale (Hamilton, 1960) related to anxiety (anxiety somatic, anxiety psychic, somatic general, agitation, insight, and hypochondriasis) were also used.

Self-report measures included the neuroticism subscale from the 60-item NEO Five-Factor Inventory – 3 (McCrae and Costa, 2010), as well as the four items that assess for anxiety and the two items that assess for panic from the Concise Associated Symptoms Tracking Scale (Trivedi et al., 2011b). Additional measures included ten items from the Anxious Arousal subscale of a 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (Wardenaar et al., 2010), one additional item from the General Distress subscale ("I worried about a lot of things") with face-validity for anxiety, and 20 questions from the state version of the Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1983), all administered before participants began their first EEG session.

Additional measures were selected for follow-up discriminant and convergent validity analyses: Anger Attacks Questionnaire (Fava et al., 1991), Altman Self-Rating Mania Scale (Altman et al., 1997), Concise Health Risk Tracking Scale (Trivedi et al., 2011a), Childhood Trauma Questionnaire (Bernstein et al., 2003), Quick Inventory of Depressive Symptoms (Rush et al., 2003), Social Adjustment Scale (Gameroff et al., 2012), and Snaith-Hamilton Anhedonia Scale (Snaith et al., 1995). All included measures are previously validated measures with strong psychometric data. In order to understand the relationship between identified factors and the clinical measures as they are used, overlapping items were not removed. All measures were scored using standard procedures.

The behavioral Flanker Task required participants to specify (via a button press) whether arrows pointed left or right; these arrows were presented alongside adjacent flankers pointed in the same (congruent) or different (incongruent) direction. Additional details about the Flanker Task's methodology have been previously described (Webb et al., 2016). Following prior research (Webb et al., 2016), main analytic variables included response time (RT) and accuracy for congruent and incongruent trials considered separately, and the Flanker interference effects, which were assessed by computing a "congruent minus incongruent" score for accuracy and an "incongruent minus congruent" score for RT, such that larger scores on both measures indicate greater interference on incongruent versus congruent trials. These effects control for individual differences in psychomotor processing speed.

2.3. Data analysis

The analyses used data from 200 participants who contributed baseline data to define anxiety/anxious factors based on items that ranged from current mood state (state items from the State Anxiety Inventory) to formal anxiety disorder diagnoses (from the SCID). Of the 200 participants, 195 had complete data on all items; therefore, this subset was included in analyses. Seven participants were missing data on the Flanker Task, leading to N = 188 for these analyses. The analyses were divided into four steps: (1) sample descriptives and demographics; (2) exploratory factor analysis to determine a set of factors

that defined patient and clinician-assessed anxiety; (3) correlations to establish factors' validity with clinical measures and (4) correlations and inferential tests to establish factors' validity with the Flanker Task.

To determine the maximum number of factors to retain, both the Velicer's minimum average partial (MAP) test (Velicer, 1976) and parallel analyses (Horn, 1965) were conducted. Both methods were used since the MAP test may underestimate and the parallel analysis may overestimate the number of factors (O'Connor, 2000). These tests indicated a maximum of five factors be retained; therefore, our principal component analyses were limited to four and five-factor solutions. In order to allow for maximum separation between the measures, the factors were rotated using the varimax orthogonal rotation method. Items were assigned to the factor with its highest factor loading, to avoid any cross-loading. Furthermore, items must have met a minimum factor loading value of 0.35 (Nunnally and Bernstein, 1994). In the initial component analyses, none of the SCID item factor loadings met the 0.35 minimum criteria for loading, with ranges between 0.17 and 0.28. Therefore, all of these items were dropped from all factor analyses.

Follow-up analysis of the factors derived from the exploratory analyses included computing item-to-item correlations and coefficient alpha values for each of the determined factors to examine internal consistency. In addition, correlations between the total scores for each of the derived anxiety factors and other clinical/behavioral measures mentioned above were conducted. Total scores were computed using the sum of the weighted items, in order to give equal weight to each of the items, since item scales were not all of the equal lengths. Pearson product-moment correlations were used to associate the anxiety factors with accuracy and RT on congruent and incongruent trials in the Flanker task, as well as the Flanker interference effects. Following prior research (Meng et al., 1992), tests for differences between the factors and correlations with Flanker effects were conducted in two steps: An overall X^2 test for differences between correlated correlation coefficients, followed by pairwise comparisons if the overall test was significant [$p < .05$ (two-tailed test)].

3. Results

3.1. Sample characteristics

Table 1 illustrates the sample's descriptive and demographic data. Participants' mean age was 37.16 years ($SD = 13.03$), while the mean number of years of education was 14.89 ($SD = 2.42$) and HAMD-17 score was 18.78 ($SD = 4.43$).

3.2. Defining anxiety factors through factor analysis

Individual items as selected above were entered into an exploratory factor analysis using varimax rotation. Results revealed five unique factors. However, the fifth factor, comprised of the lowest eigenvalue (2.49), was uninterpretable, involving items of restlessness and negative mood each comprised of individual items with loadings in opposite directions (i.e., the item "I am feeling restless, as if I have to move constantly", loaded at 0.685, while the item from the HAM-D denoting agitation loaded at −0.341). For these reasons, we re-ran analyses to force four factors. All factors demonstrated appropriate loadings and high degrees of internal consistency (see Table 2) and explained very little variance of other factors (see Supplemental Fig. 1). Four factors were indicated: Immediate (state) anxiety, physiological fear response (panic) to environmental stimuli, neuroticism/worry, and agitation and restlessness.

3.3. Intercorrelations with other baseline Clinical Characteristics

Follow-up analyses indicated correlations with similar measures in the expected direction (see Table 3). As expected, the state/immediate anxiety factor was nearly perfectly correlated with the State Anxiety Index from the State-Trait Anxiety Index but also showed medium-to-high correlations with the anxiety/somatization factor from the Hamilton Depression Rating Scale, the General Distress subscale from the Mood and Anxiety Symptom Questionnaire, and neuroticism. The panic or fear response factor was nearly perfectly correlated with the Anxious

Table 1
Descriptive and demographic information for N = 195 participants.

Variable	Frequency	Percent
Depression Chronicity[a]		
Chronic	94	48.21%
Non-Chronic	101	51.79%
Depression Severity[b]		
High	110	56.41%
Low	85	43.59%
Educational Status		
Completed Higher Education	76	39.58%
Completed Some Higher Education	69	35.94%
No Higher Education	14	7.29%
High School Diploma	20	10.42%
GED or Equivalent	7	3.65%
Did Not Graduate High School	5	2.60%
N/A	1	0.52%
Marital Status		
Single	116	60.20%
Married	39	20.21%
Divorced	30	15.54%
Separated	6	3.11%
Widowed	2	1.04%
Hispanic or Latino Origin		
No	159	81.54%
Yes	36	18.46%
Race		
White	124	63.59%
Black or African-American	45	23.08%
Asian	14	7.18%
American Indian or Alaska Native	1	0.51%
Other	11	5.64%
Gender		
Male	66	33.85%
Female	129	66.15%
Any Anxiety Disorder		
Absent	110	56.41%
Clinically Present	85	43.59%
Anxiety NOS		
Absent	173	94.54%
Clinically Present	10	5.46%
Generalized Anxiety Disorder		
Absent	163	83.59%
Sub-clinically Present	8	4.10%
Clinically Present	24	12.31%
Obsessive Compulsive Disorder		
Absent	181	93.30%
Sub-clinically Present	8	4.12%
Clinically Present	5	2.58%
Panic Disorder		
Absent	161	83.42%
Sub-clinically Present	15	7.77%
Clinically Present	17	8.81%
Specific Phobia		
Absent	148	75.90%
Sub-clinically Present	12	6.15%
Clinically Present	35	17.95%
PTSD		
Absent	165	84.62%
Sub-clinically Present	14	7.18%
Clinically Present	16	8.21%

Note. [a] = "Chronic" indicates individuals from the SCID whose depression history and course was deemed chronic, with only one or two, if any, well periods; while non-chronic indicates individuals with a single episode, recurrent, or chronic with multiple well episodes. [b] = "High severity" denotes individuals with a HAM-D 17 ≥ 20, while "low severity" denotes individuals with a HAM-D 17 < 20. Finally, for all variables where levels do not add up to 195, the differences indicate missing values.

Table 2
Factor loadings and additional psychometric information for four anxiety factors.

Measure	Item No.	Item Description	Immediate (state) Anxiety	Fear Response (panic) to Environmental Stimuli	Neuroticism/ Worry	Agitation and Restlessness
STAI	10	I feel comfortable	**−0.792**			
STAI	2	I feel secure	**−0.780**			
STAI	16	I feel content	**−0.764**			
STAI	5	I feel at ease	**−0.751**			
STAI	1	I feel calm	**−0.725**			
STAI	15	I am relaxed	**−0.714**			
STAI	20	I feel pleasant	**−0.690**			
STAI	19	I feel steady	**−0.687**			
STAI	11	I feel self-confident	**−0.662**			
STAI	8	I feel satisfied	**−0.635**			
STAI	4	I feel strained	**0.671**			
STAI	7	I am presently worrying over possible misfortunes	**0.626**			
STAI	6	I feel upset	**0.617**			
STAI	3	I am tense	**0.597**			0.327
STAI	17	I am worried	**0.594**			
STAI	18	I feel confused	**0.578**		0.336	
STAI	9	I feel frightened	**0.556**			
STAI	12	I feel nervous	**0.534**			0.338
STAI	13	I am jittery	**0.465**			0.314
STAI	14	I feel indecisive	**0.436**			
MASQ-D30	27	My heart was racing or pounding		**0.718**		
MASQ-D30	21	I was short of breath		**0.694**		
MASQ-D30	18	I had pain in my chest		**0.628**		
MASQ-D30	8	I felt dizzy or light-headed		**0.619**		
MASQ-D30	15	I was trembling or shaking		**0.595**		
CAST	12	I can feel my heart racing		**0.566**		
CAST	3	I feel as if I am going to have a heart attack		**0.539**		
MASQ-D30	30	I had trouble swallowing		**0.484**		
MASQ-D30	20	I had hot or cold spells		**0.483**		
HAM-D	11	Anxiety, somatic		**0.453**		
MASQ-D30	24	My muscles were tense or sore		**0.428**		
MASQ-D30	5	I felt nauseous		**0.420**		
MASQ-D30	2	I was startled easily		**0.401**		
NEO-FFI-3	26	Sometimes I feel completely worthless.			**0.643**	
NEO-FFI-3	41	Too often, when things go wrong, I get discouraged and feel like giving up			**0.612**	
NEO-FFI-3	6	At times I have felt bitter and resentful.			**0.548**	
NEO-FFI-3	51	I often feel helpless and want someone else to solve my problems			**0.517**	
NEO-FFI-3	36	I often get angry at the way people treat me			**0.495**	
NEO-FFI-3	56	At times I have been so ashamed I just wanted to hide			**0.490**	
NEO-FFI-3	11	When I'm under a great deal of stress, sometimes I feel like I'm going to pieces.			**0.479**	0.338
NEO-FFI-3	16	I rarely feel lonely or blue			**−0.457**	
NEO-FFI-3	31	I rarely feel fearful or anxious.			**−0.440**	**−0.410**
MASQ-D30	28	I worried about a lot of things			**0.416**	
NEO-FFI-3	1	I am not a worrier.			**−0.401**	
CAST	15	I cannot sit still				**0.679**
CAST	6	I am feeling restless, as if I have to move constantly				**0.654**
CAST	11	I feel very tense and I cannot relax.				**0.651**
NEO-FFI-3	21	I often feel tense and jittery.				**0.571**
CAST	1	I feel anxious all the time			0.303	**0.550**
* HAM-D	20	Anxiety Psychic				0.317
NEO-FFI-3	46	I am seldom sad or depressed				**0.392**
Eigenvalue			9.11	4.78	3.75	3.59
Percent Variance Explained			16.56	8.69	6.82	6.53
Coefficient Alpha			0.92	0.82	0.75	0.63

Note. CAST, Concise Associated Symptoms Tracking Scale; HAM-D, The Hamilton Rating Scale for Depression; MASQ-D30, Mood and Anxiety Symptoms Questionnaire; NEO-FFI-3, NEO Five-Factor Inventory-3; STAI, The State-Trait Anxiety Inventory. Items in bold indicate on what factor the item was included. * = item not included in any factor, due to loading below 0.35.

Arousal subscale from the Mood and Anxiety Symptom Questionnaire but also demonstrated medium-to-high correlations with the 10-item General Distress subscale from the Mood and Anxiety Symptom Questionnaire. As the state/immediate anxiety factor was wholly comprised of the State Anxiety Index, it measures exclusively symptoms assessed by this instrument.

The neuroticism and worry factor was, as expected, nearly perfectly correlated with neuroticism but also demonstrated high correlations with General Distress and with the propensity for suicidality subscale of the Concise Health Risk Tracking scale, which denotes low levels of

Table 3
Intercorrelations between each of the four factors and additional items/measures for convergent and discriminant validity.

Variables	Immediate/State Anxiety Factor	Fear (Panic) Factor	Neuroticism and Worry Factor	Restlessness and Agitation Factor
State Anxiety Factor	–			
Panic Factor	.27***	–		
Neuroticism and Worry Factor	.37***	.23**	–	
Restlessness/Agitation Factor	.36***	.40***	.26***	–
AAQ Score	.07	.26***	.15*	.36***
ASRM Score	.00	.04	−.06	.16*
CAST Total	.29***	.49***	.26***	.78***
CAST Anxiety	.33***	.40***	.25***	.94***
CAST Insomnia	.12	.05	.10	.20**
CAST Irritability	.29***	.41***	.35***	.58***
CAST Mania	−.09	.06	−.17*	.26***
CAST Panic	.20**	.58***	.17*	.27***
CHRT Propensity Score	.28***	.22**	.53***	.24***
CHRT Risk Score	.17**	.29***	.26***	.35***
CTQ Emotional Abuse	.19**	.21**	.26***	.18*
CTQ Emotional Neglect	.17*	.19**	.16*	.18*
CTQ Physical Abuse	.14*	.13*	.02	.09
CTQ Physical Neglect	.29***	.24***	.16*	.23**
CTQ Sexual Abuse	.08	.16*	.20**	−.02
HAM-D 17 item	.38***	.32***	14	24***
MASQ Anxious Arousal	.25***	.96***	.21**	.36***
MASQ Anhedonic Depression	.29***	.04	.27***	.00
MASQ General Distress	.39***	.38***	.62***	.23***
NEO-FFI-3 Agreeableness	−.04	−.12*	−.23***	−.22**
NEO-FFI-3 Conscientiousness	−.14*	.05	−.41***	.03
NEO-FFI-3 Extraversion	−.12*	.19**	−.26***	.11
NEO-FFI-3 Neuroticism	.34***	.21**	.96***	.23**
NEO-FFI-3 Openness	−.09	.18*	.01	−.08
QIDS Total	.29***	.32***	.24***	.22**
SAS Mean	.24***	.17*	.37***	.13*
SHAPS Total	.18**	.18**	.14	.01
STAI Score	.99***	.28***	.40***	.38***
Any Anxiety Disorder	.15*	.16*	.04	.22**

Note. *$p < .05$, **$p < .01$, ***$p < .001$.
AAQ, Anger Attacks Questionnaire; ASRM, Altman Self-Rating Mania Scale; CAST, Concise Associated Symptoms Tracking Scale; CHRT, Concise Health Risk Tracking Scale; CTQ, Childhood Trauma Questionnaire; HAM-D, The Hamilton Rating Scale for Depression; MASQ, Mood and Anxiety Symptoms Questionnaire; NEO-FFI-3, NEO Five-Factor Inventory-3; QIDS, Quick Inventory of Depressive Symptoms; SAS, Social Adjustment Scale; SHAPS, Snaith-Hamilton Anhedonia Scale; STAI, State Anxiety Inventory.

social support and high degrees of hopelessness, and a medium correlation with the Social Adjustment Scale. Finally, the agitation and restlessness factor demonstrated a medium correlation with the Anger Attacks Questionnaire, Anxious Arousal subscale of the Mood and Anxiety Symptom Questionnaire, and the risk subscale of the Concise Health Risk Tracking Scale, which denotes active suicidal ideation. These correlations are logical, given this factor's emphasis on agitation and restlessness. Of particular note, generally medium or small-to-medium correlations were observed between the factors. Factors were generally correlated with the presence of any anxiety disorder from the SCID, but only at a small-to-nonsignificant level. Finally, discriminant validity was established by the presence of nonsignificant or small degrees of correlations between many of the factors and unrelated symptom profiles, such as anhedonia and mania, which are more characteristic of unipolar/bipolar depressive disorders rather than anxiety disorders/symptoms.

3.4. Validation with Flanker Task

When considering Flanker data, RT was faster and accuracy higher, on congruent (*M*_RT: 373.53 ms, *SD*_RT: 56.69 ms, accuracy: 96.41%) as compared to incongruent trials (*M*_RT: 434.19 ms, *SD*_RT: 70.57 ms, accuracy: 75.20%), indicating that the task elicited the intended effects. Additional results indicated that the panic factor was associated with increased RT (slower performance), and the neuroticism/worry factor was associated with decreased RT (faster performance), in both congruent and incongruent trials (Table 4). State Anxiety and Restlessness/Agitation were consistently unassociated with Flanker Task RT or accuracy. Only the neuroticism/worry factor was significantly associated with Flanker interference effects on RT and accuracy. Specifically, higher scores on neuroticism/worry were associated with greater interference effect on accuracy but reduced interference effect on RT (Fig. 1). Thus, individuals with greater neuroticism/worry made more mistakes in response to incongruent vs. congruent trials but without showing the expected slowing when responding to incongruent vs. congruent trials.

To further elucidate these findings, the overall test for differences between the size of correlation for the four factors and the Flanker interference (accuracy) was not significant (X^2 (3) = 5.58, $p > .05$). However, the overall test was statistically significant for the Flanker interference on RT ($X^2(3) = 9.97$, $p < .05$). Pairwise tests indicated the correlation between the neuroticism/worry factor and Flanker interference (RT) was significantly greater than that between Flanker interference RT and all other factors (Immediate Anxiety: Z = 2.38, Panic: Z = 2.86, Restlessness and Agitation: Z = 2.91). These results indicate that only the neuroticism/worry factor was significantly related to Flanker Task interference, and, in the case of RT, significantly more so than all other factors.

4. Discussion

This study provides evidence for four distinct anxiety symptom factors – current emotional response, physiological fear/panic response to environmental stimuli, neuroticism/worry, and agitation/restlessness in a large sample of outpatients with depression. Convergent validity of these factors was well-established through intercorrelations with other clinical measures of anxiety (panic/anxiety; general distress; anxious arousal; neuroticism, state anxiety). As a further test of validity, we determined that the fear/panic and neuroticism/worry factors were associated with performance on the Flanker Task, such that higher scores on fear/panic were associated with increased response time (RT), and that higher scores on neuroticism/worry were associated with reduced RT and impaired task accuracy. No relationship on Flanker Task RT or accuracy occurred among the State Anxiety and Restlessness/Agitation factors, further suggesting differential effects and also demonstrating a unique finding of how the Flanker Task was associated with some subtypes of anxiety but not others. Prior EMBARC-study research (Webb et al., 2016) determined that neuroticism – as assessed by the NEO neuroticism subscale – was not significantly correlated with Flanker task performance; the different results might be due to the divergent ways in which neuroticism/worry was defined in the Webb study as opposed to ours, and especially due the increase in sample size (and therefore power) in our study.

Most importantly, these results suggest that there is not a single unidimensional symptom factor that can define anxiety. Our anxiety factors describe unique components of anxiety among depressed outpatients, including immediate state anxiety; physiological components of anxiety akin to panic; cognitive aspects of anxiety, including worry, fear, and helplessness; and psychomotor and cognitive restlessness/agitation. Of particular interest, state anxiety factor was fully explained by a single measure: The State Anxiety Inventory. Furthermore, two of these factors, panic/fear, and neuroticism/worry, were associated with performance on the Flanker Task, which measured response inhibition and cognitive control. Taken together, our results indicate that using only a single measure to capture anxiety would limit examination of the variability of how anxiety among depressed outpatients is experienced and demonstrates how components of anxiety among depressed outpatients are differentially associated with impaired cognitive control. It is important to note very high correlations were observed between the state anxiety factor and the STAI; between the panic/fear factor and the Anxious Arousal subscale from the MASQ, and between the neuroticism/worry factor and the neuroticism subscale of the NEO. Therefore, clinicians may consider using the single measures referenced above for the sake of clinical utility and parsimony.

One major advantage of our study lies in the use of self-report, clinician-rated, and behavioral data (for validation purposes). No diagnostic anxiety disorder from the SCID loaded on any specific factor. Although eligibility criteria excluded participants with current primary anxiety diagnoses, 43.6% of patients were diagnosed with a current or lifetime anxiety disorder diagnosis. Therefore, these findings suggest that specific DSM-defined anxiety disorders may represent something distinct from the four anxiety factors identified in our study. Anxiety disorders per diagnostic criteria are inherently heterogeneous, with any two people meeting criteria for the same disorder potentially having vastly different symptom profiles.

Another important study finding was linking discrete anxiety symptom factors and differential patterns of response in the Flanker Task, whereby some factors were not associated with task accuracy or RT, while others were. Specifically, neuroticism/worry was uniquely associated with Flanker Task interference (i.e., greater accuracy but reduced RT interference, perhaps due to a speed-accuracy trade-off), while fear/panic was associated with slower RT, and neuroticism/worry with faster RT, further differentiating these factors. These results suggest heterogeneous subgroups of anxiety within depressed outpatients, and that these subgroups might be associated with different underlying biology – a question for future research – with differential effects on task performance.

By determining unique factors that capture physiological and psychological anxiety, the current study is in line with prior research focused exclusively on anxiety (Lang et al., 2000), yet extends this research on anxiety classification into a sample of outpatients with primary depression. We predict that physiological and psychological forms of anxiety will differentially manifest in other forms of behavior beyond the current study; therefore, our findings suggest areas for future research. In subsequent research, we plan (a) to test our four anxiety factors alongside both resting and task-based neuroimaging data to better understand the differences in physiological and brain systems implicated in each of these components of anxiety and (b) to analyze whether depression treatment outcomes are predicted by baseline levels of various anxiety factors. Such research may situate these distinct anxiety components closer to the concept of endophenotypes (Insel and Cuthbert, 2009).

Table 4
Correlations between each of the four factors and both RT and accuracy from the Flanker Task (N = 188).

Variables	Immediate/State Anxiety Factor	Fear (Panic) Factor	Neuroticism and Worry Factor	Restlessness and Agitation Factor
Mean RT on congruent trials[a]	−.14+	.17*	−.16*	.03
Accuracy on congruent trials[b]	.07	−.02	.06	.01
Mean RT on incongruent trials	−.07	.15*	−.19**	.04
Accuracy on incongruent trials	.08	.03	−.08	.02
Flanker interference (RT)[c]	.07	.04	−.23**	.03
Flanker interference (accuracy)[d]	−.01	−.03	.19*	.04

Note. + p < .10, *p < .05, **p < .01.
[a] Calculated in ms.
[b] Computed as percent correct responses.
[c] Flanker interference (RT) = RT(incongruent) – RT(congruent).
[d] Flanker interference (accuracy) effect = Accuracy(congruent) – Accuracy(incongruent).

There are a number of strengths of the current study, including a relatively large sample size across several geographically-diverse sites within the United States, advanced analytic techniques, and the inclusion of well-validated clinician and self-report measures of anxiety. The main limitation is the exclusion of participants with primary anxiety disorders; however, almost 44% of participants had either a current or a lifetime anxiety disorder diagnosis based on a structured clinical interview. Additional limitations include the inclusion of particular measures at time points where anxiety may already be relatively higher (i.e., before an EEG), the use of incomplete measures (i.e., only the state subscale of the State-Trait Anxiety Inventory), and the facts that no biological measures were included and that only participants with major depressive disorder and/or dysthymia were included, limiting the ability to take a fully RDoC-based, transdiagnostic framework to this study. Nonetheless, the current study capitalizes on a range of measures of varying types and administration procedures in order to more comprehensively investigate the nature of anxiety than traditional research that has relied only on single measures of anxiety, or only anxiety disorder diagnoses.

Our findings support an approach to anxiety that examines anxiety not as distinct disorders nor as unidimensional, but instead as represented through separate dimensions encoding cognitive, physiological, and psychological components, as assessed by several self-report and clinician-assessed instruments. Future research should associate these factors with genetic, physiological, and additional behavioral data beyond those explored in this manuscript, as well as antidepressant treatment outcomes. Future research should also explore whether these anxiety subgroups might serve as antidepressant treatment moderators.

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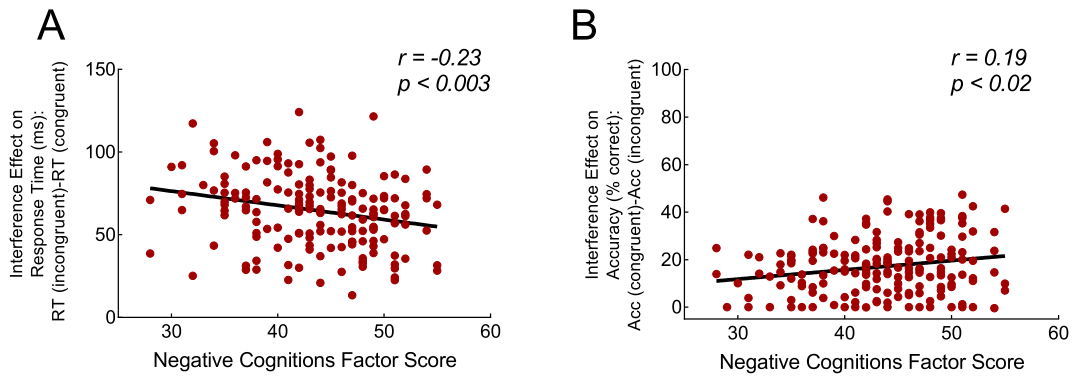

Fig. 1. Correlations between neuroticism/worry factor score and Flanker interference effects when considering (A) response time and (B) accuracy.

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Appendix A. Supplementary data

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References

Altman, E.G., Hedeker, D., Peterson, J.L., Davis, J.M., 1997. The altman self-rating mania scale. Biol. Psychiatr. 42 (10), 948–955.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the childhood trauma questionnaire. Child Abuse Negl. 27 (2), 169–190.

Chen, S., Yao, N., Qian, M., Lin, M., 2016. Attentional biases in high social anxiety using a flanker task. J. Behav. Ther. Exp. Psychiatr. 51, 27–34.

Cuthbert, B.N., 2014. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatr.: official journal of the World Psychiatric Association (WPA) 13 (1), 28–35.

Etkin, A., Schatzberg, A.F., 2011. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. Am J Psychiatry 168 (9), 968–978.

Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion 7 (2), 336–353.

Farber, I.E., Spence, K.W., 1956. Effects of anxiety, stress, and task variables on reaction time. J. Pers. 25 (1), 1–18.

Fava, M., Rosenbaum, J.F., McCarthy, M., Pava, J., Steingard, R., Bless, E., 1991. Anger attacks in depressed outpatients and their response to fluoxetine. Psychopharmacol. Bull. 27 (3), 275–279.

Fava, M., Rush, A.J., Alpert, J.E., Balasubramani, G.K., Wisniewski, S.R., Carmin, C.N., Biggs, M.M., Zisook, S., Leuchter, A., Howland, R., Warden, D., Trivedi, M.H., 2008. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am. J. Psychiatr. 165 (3), 342–351.

First, M.B.S.R.L., Gibbson, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-iv-tr Axis I Disorders, Research Version, Patient Edition with Psychotic Screen. Biometrics Research. New York State Psychiatric Institute New York.
Gameroff, M.J., Wickramaratne, P., Weissman, M.M., 2012. Testing the short and screener versions of the social adjustment scale-self-report (SAS-SR). Int. J. Meth. Psychiatr. Res. 21 (1), 52–65.
Gentes, E.L., Dennis, P.A., Kimbrel, N.A., Rissling, M.B., Beckham, J.C., Calhoun, P.S., 2014. DSM-5 posttraumatic stress disorder: factor structure and rates of diagnosis. J. Psychiatr. Res. 59, 60–67.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Horn, J.L., 1965. A rationale and test for the number of factors in factor analysis. Psychometrika 30, 179–185.
Huyser, C., Veltman, D.J., Wolters, L.H., de Haan, E., Boer, F., 2011. Developmental aspects of error and high-conflict-related brain activity in pediatric obsessive-compulsive disorder: a fMRI study with a Flanker task before and after CBT. J. Child Psychol. Psychiatry Allied Discip. 52 (12), 1251–1260.
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatr. 167 (7), 748–751.
Insel, T.R., Cuthbert, B.N., 2009. Endophenotypes: bridging genomic complexity and disorder heterogeneity. Biol. Psychiatr. 66 (11), 988–989.
Iza, M., Wall, M.M., Heimberg, R.G., Rodebaugh, T.L., Schneier, F.R., Liu, S.M., Blanco, C., 2014. Latent structure of social fears and social anxiety disorders. Psychol. Med. 44 (2), 361–370.
Kocovski, N.L., Endler, N.S., Cox, B.J., et al., 2004. The differential assessment of state-trait anxiety and depression in a clinically anxious sample. J. Psychopathol. Behav. Assess. 26 (3), 165–172.
Lang, P.J., Davis, M., Ohman, A., 2000. Fear and anxiety: animal models and human cognitive psychophysiology. J. Affect. Disord. 61 (3), 137–159.
McCrae, R.R., Costa, P.T., 2010. NEO Inventories for the NEO Personality Inventory-3 (NEO-pi-3), NEO Five-factor Inventory-3 (NEO-ffi-3), NEO Personality Inventory-revised (NEO-pi-r): Professional Manual PAR, Lutz, FL.
Meng, X.-L., Rosenthal, R., Rubin, D.B., 1992. Comparing correlated correlation coefficients. Psychol. Bull. 111, 172–175.
Nunnally, J.C., Bernstein, I.H., 1994. In: Psychometric Theory, third ed. McGraw-Hill, New York, NY.
O'Connor, B.P., 2000. SPSS and SAS programs for determining the number of components using parallel analysis and velicer's MAP test. Behav. Res. Methods Instrum. Comput. 32 (3), 396–402.
Robinson, O.J., Vytal, K., Cornwell, B.R., Grillon, C., 2013. The impact of anxiety upon cognition: perspectives from human threat of shock studies. Front. Hum. Neurosci. 7, 203.
Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatr. 54 (5), 573–583.
Shear, M.K., Brown, T.A., Barlow, D.H., Money, R., Sholomskas, D.E., Woods, S.W., Gorman, J.M., Papp, L.A., 1997. Multicenter collaborative panic disorder severity scale. Am. J. Psychiatr. 154 (11), 1571–1575.
Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br. J. Psychiatry 167 (1), 99–103.
Spielberger, C.D., Gorsuch, R.L., Lushene, R., Vagg, P.R., Jacobs, G.A., 1983. Manual for the State-trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Spitzer, R.L., Kroenke, K., Williams, J.B., Lowe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097.
Trivedi, M.H., McGrath, P.J., Fava, M., Parsey, R.V., Kurian, B.T., Phillips, M.L., Oquendo, M.A., Bruder, G., Pizzagalli, D., Toups, M., Cooper, C., Adams, P., Weyandt, S., Morris, D.W., Grannemann, B.D., Ogden, R.T., Buckner, R., McInnis, M., Kraemer, H.C., Petkova, E., Carmody, T.J., Weissman, M.M., 2016. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): rationale and design. J. Psychiatr. Res. 78, 11–23.
Trivedi, M.H., Wisniewski, S.R., Morris, D.W., Fava, M., Gollan, J.K., Warden, D., Nierenberg, A.A., Gaynes, B.N., Husain, M.M., Luther, J.F., Zisook, S., Rush, A.J., 2011a. Concise Health Risk Tracking scale: a brief self-report and clinician rating of suicidal risk. J. Clin. Psychiatr. 72 (6), 757–764.
Trivedi, M.H., Wisniewski, S.R., Morris, D.W., Fava, M., Kurian, B.T., Gollan, J.K., Nierenberg, A.A., Warden, D., Gaynes, B.N., Luther, J.F., Rush, A.J., 2011b. Concise Associated Symptoms Tracking scale: a brief self-report and clinician rating of symptoms associated with suicidality. J. Clin. Psychiatr. 72 (6), 765–774.
Velicer, W.F., 1976. Determining the number of components from the matrix of partial correlations. Psychometrika 41, 321–327.
Wardenaar, K.J., van Veen, T., Giltay, E.J., de Beurs, E., Penninx, B.W., Zitman, F.G., 2010. Development and validation of a 30-item short adaptation of the mood and anxiety symptoms questionnaire (MASQ). Psychiatr. Res. 179 (1), 101–106.
Webb, C.A., Dillon, D.G., Pechtel, P., Goer, F.K., Murray, L., Huys, Q.J., Fava, M., McGrath, P.J., Weissman, M., Parsey, R., Kurian, B.T., Adams, P., Weyandt, S., Trombello, J.M., Grannemann, B., Cooper, C.M., Deldin, P., Tenke, C., Trivedi, M., Bruder, G., Pizzagalli, D.A., 2016. Neural correlates of three promising endophenotypes of depression: evidence from the EMBARC study. Neuropsychopharmacology 41 (2), 454–463.