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Positive and negative valence systems in major depression have distinct clinical features, response to antidepressants and relationships with immunomarkers

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Abstract

Background: Heterogeneity in major depressive disorder (MDD) is well recognized but not well understood. Core depressive features are reward and emotional symptoms, which reflect dysfunctions in the positive valence (PV) and negative valence (NV) systems, respectively. This study assessed whether PV and NV systems (based on selected symptoms) were associated with different clinical features, antidepressant response and levels of immunomarkers in adults with MDD.

Methods: These analyses used data from the Combining Medications to Enhance Depression Outcomes (CO-MED) study (N=665; n=166 for immunomarkers). PV and NV symptom scores were extracted from the clinician-rated 30-item Inventory of Depressive Symptomatology. Correlational analyses were conducted.

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Conflict of Interest Statement

Dr. Rush has received consulting fees from Akili, Brain Resource Inc., Compass Inc., Curbstone Consultant LLC., Emmes Corp, Holmusk, Inc., Liva-Nova, Sunovion, Takeda USA, Taj Medical; speaking fees from Liva-Nova; royalties from Guilford Press and the University of Texas Southwestern Medical Center, Dallas, TX. (for the Inventory of Depressive Symptoms and its derivatives). He is also named co-inventor on two patents: U.S. Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS and U.S. Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S. **Dr. Jha** has received contract research grant from Acadia Pharmaceutical and Janssen Research. **Dr. Trivedi** has received research support from NIMH, NIDA, J&J, Janssen Research and Development LLC; has served as a consultant for Alkermes Inc., Allergan, Arcadia Pharmaceuticals Inc., AstraZeneca, Lundbeck, Medscape, MSI Methylation Sciences Inc., Merck, Otsuka America Pharmaceuticals Inc., and Takeda Pharmaceuticals Inc. **Dr. Carmody** has received an honorarium from the University of Texas San Antonio. **Dr. Trombello** currently owns stock in Merck and Gilead Sciences and within the past 36 months previously owned stock in Johnson & Johnson. **Drs. Medeiros, Furman**, **Czysz**, and **Cooper** have no conflicts to report.

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Results: PV and NV symptom scores were substantially associated with different clinical features. PV symptoms (impaired motivation, impaired energy and anhedonia) were independently associated with female gender (p<.001), older age (p=.012), and higher cognitive and physical impairment (p<.001) according to the 7-item Cognitive and Physical Functioning Questionnaire. Conversely, NV symptoms (anxiety and interpersonal sensitivity) were independently associated with younger age (p=.013), more anxious comorbidities (p=.001 for GAD, p=.002 for social phobia) and other commonly associated non criterion symptoms (p<.001). Overall, PV symptoms were more responsive to antidepressants than NV symptoms (p<.0001; Cohen's d=0.455). A PV symptom score was positively correlated with the concentration of three pro-inflammatory and one anti-inflammatory factors. In contrast, a NV symptom score was negatively associated with only one pro-inflammatory immunomarker.

Conclusions: PV and NV system function appears to be reflected in selected clinical symptoms that differentially relate to other clinical features, treatment outcomes and immunological function.

Keywords

depression; major depressive disorder; RDoC; positive valence; negative valence; immunomarkers; biomarkers

1. Introduction

Despite the high prevalence and long history of research, heterogeneity of major depressive disorder (MDD) has not been fully understood. While several treatment options are available, selecting the "right" treatment for an individual has not been possible (Otte et al., 2016; Rush et al., 2009; Trivedi et al., 2016). Previous attempts to operationalize the different depressive presentations in clinical subtypes (melancholic, atypical, anxious) have had limited success (Arnow et al., 2015; Rush et al., 2009; Uher et al., 2011). The lack of biological markers either to support previous clinical classifications or by which to select treatment is also a major limitation (Insel et al., 2010; Rush & Ibrahim, 2018). Consequently, clinical practice presently relies on a try and try again approach to personalizing treatment selection (Gaynes et al., 2009; Rush & Ibrahim, 2018; Rush et al., 2009). Assessment of brain systems (alternatively referred to as functional domains) is a promising method for understanding the heterogeneity of mental disorders. The system-based approach is more consistent with the latent pathophysiology, has been well validated in basic science and can be readily applied to mood and other mental disorders (Insel et al., 2010; Woody & Gibb, 2015).

Emotional dysfunctions such as anhedonia and dysphoria are core symptoms of MDD (Otte et al., 2016; Russo & Nestler, 2013). Therefore, the systems responsible for reward and emotional responses [i.e. positive valence (PV) and negative valence (NV) systems] may be critical to understanding MDD (Woody & Gibb, 2015). PV systems modulate response to positive contexts or situations such as consummatory behavior, response to reward, motivation, engagement and interest (Craske, Meuret, Ritz, Treanor, & Dour, 2016; Cuthbert & Insel, 2013; Dillon et al., 2014; Morris & Cuthbert, 2012; Nusslock & Alloy, 2017), and engage the ventral tegmental area, nucleus accumbens, as well as fronto-striatal pathways (Craske et al., 2016; Dillon et al., 2014; Kringelbach, 2005; Nusslock & Alloy, 2017; Russo

& Nestler, 2013). Conversely, NV systems are associated with responses to aversive and unpleasant contexts or situations such as anxiety, fear, phobia, and loss (Cuthbert & Insel, 2013; Dillon et al., 2014; Morris & Cuthbert, 2012; Nusslock & Alloy, 2017). NV systems involve the amygdala, insula and the striatum (Dillon et al., 2014; Nusslock & Alloy, 2017). Both the PV and NV systems can be studied from different perspectives such as genes, molecules, circuits, physiology, behavior, and self-report (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012).

Functional neuroimaging studies suggest that both PV and NV systems operate differently in depressed individuals versus non-depressed individuals (J. P. Hamilton et al., 2012; Pizzagalli, 2014). Previous fMRI research has found that depressed patients had a lower activation of brain regions associated with PV systems during reward tasks (e.g. the nucleus accumbens, the ventral striatum and the orbitofrontal cortex) as compared to healthy controls (Pizzagalli, 2014). On the other hand, several studies have found greater baseline response on fMRI of neurological areas related to NV systems (such as the amygdala and the anterior insula) in depressed people when compared to non-depressed individuals (J. P. Hamilton et al., 2012).

Previous literature also suggests that some MDD patients present with a pro-inflammatory state and cytokines may selectively affect specific brain systems (Dowlati et al., 2010; Miller & Raison, 2016). Elevated levels of pro-inflammatory markers, such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), IL (interleukin) 1 beta (β), and IL-6 have all been linked to MDD (Dowlati et al., 2010; Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimaki, 2015). However, there are unresolved inconsistencies as other studies have failed to find an association between these same inflammatory cytokines and MDD (Dowlati et al., 2010; Haapakoski et al., 2015). Given the heterogeneity of depression, it is likely that only a subset of depressed individuals or only some selected symptoms are associated with the pro-inflammatory state (Jha, Minhajuddin, Gadad, Greer, et al., 2017; Miller & Raison, 2016; Uher et al., 2014).

PV symptoms may represent a symptom-dimension more closely associated with inflammation. Evidence from animal and human studies indicates that specific PV symptoms (such as anhedonia and motivation) and their respective brain circuits may be modulated by immunological processes (De La Garza, 2005; Eisenberger et al., 2010; Felger et al., 2016). In humans, the administration of low doses of bacterial endotoxin (a pro-inflammatory substance) was associated with a less pronounced functional response in the reward system (Eisenberger et al., 2010), and systemic inflammation (reflected by higher concentrations of peripheral immunomarkers) was correlated with anhedonia and lower connectivity in the reward circuit (Felger et al., 2016). The link between PV symptoms and immunological changes may be mediated by a decreased ventral-striatum response induced by pro-inflammatory cytokines (Felger et al., 2016). There is a significant body of work suggesting that inflammation would primarily impact dopaminergic pathways, and is “associated with a reorganization of motivational priorities” leading to environmental withdrawal, i.e. would primarily impact PV systems (Vichaya & Dantzer, 2018). Conversely, studies linking NV symptoms to a pro-inflammatory state are more scarce and equivocal (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017; Toker, Shirom, Shapira,

Berliner, & Melamed, 2005). In this context, it is possible that immunomarkers differently affect the emotional dimensions of depression (i.e. PV and NV). A differential association of these systems with systemic inflammation may guide therapies specifically targeting one symptom dimension such as the use of anti-inflammatory therapies to better manage PV symptoms.

This study addressed the heterogeneity of MDD by using selected self-reported symptoms to reflect brain systems and evaluating clinical and laboratory based correlates. Specifically, we investigated the relationship(s) between PV and NV system function (as assessed by symptom scores), other clinical features, treatment responsiveness and relationship with immunomarkers. Clinical data were assessed in 665 participants with MDD from the Combining Medications to Enhance Depression Outcomes (CO-MED) study (Rush et al., 2011), and immunomarkers were evaluated in the subset of 166 participants who participated in the optional biomarker study.

This study addressed the following questions:

1. Is it possible to operationalize the concepts of PV and NV symptoms in a concise and clinician-friendly manner?
2. Are either PV or NV total symptom scores associated with different clinical features?
3. Do PV and NV symptoms respond differently to antidepressant treatments?
4. At the molecular level, are PV and NV symptom scores differentially associated with immunological profiles?

2. Method

2.1 Participants and recruitment

CO-MED (clinicaltrial.gov identifier NCT00590863) was a single-blind, randomized, placebo-controlled clinical trial that investigated the relative efficacy of three pharmacological treatments for MDD: escitalopram + placebo, escitalopram + bupropion, and venlafaxine-XR + mirtazapine. Between March 2008 and September 2009, 665 outpatients with non-psychotic MDD were recruited from 15 sites (nine psychiatric and six primary care clinics). Inclusion criteria for the study were: 1) age between 18 and 75 years old; 2) DSM-IV-TR criteria for either chronic (current episode lasting 2 or more years) or recurrent MDD (with current episode lasting at least two months); 3) minimum score of 16 on the 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) (M. Hamilton, 1960); and 4) no current use of psychotropic medications. The study protocol excluded individuals with any psychotic illness, lifetime bipolar disorder, current substance use disorder, need for hospitalization or presence of medical conditions that precluded the use of the study medications. The trial was approved by the Institutional Review Boards at UT Southwestern Medical Center at Dallas, the University of Pittsburgh Data Coordinating Center, each participating regional center, and all relevant clinics. Written informed consent was obtained from all subjects. See Rush et al. (2011) for further details.

In August 2008, a study examining blood-based biomarkers and treatment response was added to the original protocol. Participation in this add-on investigation was optional, and a second written informed consent was required. 166 participants consented and provided blood specimens at baseline. A previous report (Jha, Minhajuddin, Gadad, & Trivedi, 2017) detailed that individuals who did not provide blood (n = 499) were younger (mean age = 44.5 years versus 42.1; $p = .030$) and had a lower rate of statin use (20.5% versus 13.6% $p = .034$). However, no additional differences were found across demographic or clinical features.

2.2 Clinical measurements

MDD diagnosis, recurrent/chronic status and age at onset were examined by interview and confirmed by a research coordinator using the DSM-IV-based symptom checklist. We identified ~~potential~~ the items for PV and NV symptom scores *a priori* based on their face value and capacity to represent the concepts of PV and NV systems, while disregarding outcomes and other system function measurements. Items were identified from the Inventory of Depressive Symptomatology - Clinician Version (IDS-C_{30}), which evaluates 30 MDD symptoms using item scores from 0 (less severe) to 3 (more severe) (IDS-QIDS, 2018; Mapi Research Trust, 2018; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The items selection followed the NIMH definitions for PV and NV systems (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012). Therefore, items that were chosen for the PV symptom score had to assess symptoms associated with “responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning”, and included the domains reward responsiveness (reward anticipation, initial response to reward, reward satiation), reward learning (probabilistic and reinforcement learning, reward prediction error, and habit), and reward valuation (reward probability, delay, effort). Similarly, items selected for the NV symptom score had to examine “responses to aversive situations or context, such as fear, anxiety, and loss” and included the domains acute threat (fear), potential threat (anxiety), sustained threat, loss, and frustrative nonreward.

Items included to reflect PV systems were: 1) (impaired) capacity for pleasure or enjoyment (excluding sex); 2) (impaired) general interest; 3) (impaired) response of mood to desired events (mood reactivity); 4) (impaired) energy level; and 5) (impaired) interest in sex. Items included to reflect NV systems were: 1) feeling anxious or tense; 2) panic/phobic symptoms; and 3) interpersonal sensitivity. We then created two scales (representing PV and NV symptom scores) by summing the individual symptom score for each item in the component. PV symptom score (based on five items), therefore, ranged from 0 to 15, whereas NV symptom score (based on three items) ranged from 0 to 9.

We assessed specific MDD symptoms and overall symptom severity with the HAM-D_{17}, the 16-item Quick Inventory of Depressive Symptomatology Self Report Version (QIDS-SR_{16}), and the 30-item Inventory of Depressive Symptomatology (IDS-C_{30}), from which we extracted the 16-item Quick Inventory of Depressive Symptomatology Clinician Version (QIDS-C_{16}) (IDS-QIDS, 2018; Mapi Research Trust, 2018; Rush et al., 2003). When analyses were performed between PV and NV symptom scores and severity of other depressive symptoms (e.g. depressed mood, cognitive impairment, neuro-vegetative

symptoms, etc.), we used modified versions of the QIDS-C_{16} and IDS-C_{30} to assess severity. In these cases, any items assessing PV and NV were excluded (i.e. QIDS-C_{14} and IDS-C_{22}). All severity assessments measured MDD symptoms over the past week.

We assessed MDD-associated symptoms (e.g., irritability, anxiety, mania, insomnia and panic) using the 16-item Concise Associated Symptoms Tracking (CAST) Scale – Clinician Version (Trivedi et al., 2011). In addition, participants completed the following self-report questionnaires: 1) the 5-item Work and Social Adjustment Scale to examine current functional impairment (Mundt, Marks, Shear, & Greist, 2002); 2) the 7-item Cognitive and Physical Functioning Questionnaire to investigate cognitive and executive performance in the past month (Fava, Iosifescu, Pedrelli, & Baer, 2009); 3) the 125-item Psychiatric Diagnostic Screening Questionnaire to assess current psychiatric comorbidities (Rush et al., 2005); and 4) the 36-item Self-Administered Comorbidity Questionnaire to investigate current medical comorbidities (Sangha, Stucki, Liang, Fossel, & Katz, 2003).

2.3 Biospecimen Collection and Processing

Whole blood was collected in EDTA-coated tubes and transported overnight at room temperature from the site of collection to the Biological Core of the National Institute of Mental Health Repository and Genomics Resource (NIMH RGR). Plasma was extracted via centrifugation (at 2500 rcf for 10 min) at room temperature and stored at −80°C at NIMH RGR. Upon request, plasma samples were transported on dry ice to the University of Texas Southwestern Medical Center and stored at −80°C until further assayed.

2.4 Immunomarkers

In samples from the subset of participants who provided blood (n = 166), we evaluated several immunomarkers previously demonstrated to be associated with MDD, including: CRP, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α (Dowlati et al., 2010; Haapakoski et al., 2015; Miller & Raison, 2016; Otte et al., 2016). Immunomarkers were categorized into one of two groups according to their inflammatory properties: 1) primarily pro-inflammatory; or 2) primarily anti-inflammatory (Cicchese et al., 2018; You et al., 2011).

Immunomarkers were measured in a blinded fashion with either the Bio-Plex Pro Human Acute Phase 4-plex kit (#171a4010m) or Bio-Plex Pro Human Cytokine Standard 27-plex kit (#m500kcaf0y), both acquired from Bio-Rad Laboratories, Hercules, CA, USA. A Bio-Rad Bioplex Magpix 200 machine equipped with Bioplex Manager software was used to quantify immunological factors. The details about all immunomarkers assessed by the kits including assay characteristics are available (Bio-Rad Laboratories, 2016). Intra and inter-assays variations were below 10%, and samples were within the detection ranges established by the manufacturer.

2.5 Statistical analyses

Correlation analyses between the total PV and NV symptom scores and IDS-C_{22} individual items determined whether we had inadvertently excluded items that were highly correlated with PV and NV symptom scores. Internal consistency was assessed with Cronbach's alpha.

A confirmatory factor analysis was done where the items selected for the PV and NV symptom scores was divided into 2 sets of items as defined for the PV and NV scores.

To explore the association between PV and NV symptom scores and other clinical features, univariate and multivariate analyses were performed. In the univariate analyses, t-tests and Pearso's correlation coefficients were used for categorical and continuous variables, respectively. Analyses of covariance (ANCOVA) and Pearson's partial correlation coefficients were used to control results for age and MDD overall severity (QIDS-C_{14}), variables that tend to affect clinical presentation (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010; Kessler & Walters, 1998). With respect to the multivariate analyses, linear regressions were conducted to determine the variables that were independently associated with PV and NV symptom scores. In these procedures, we included demographics and clinical features with $p < .10$ in the univariate analysis after controlling for age and QIDS-C_{14}. Effect sizes were reported as standardized regression coefficients.

We used a repeated measures mixed-effects model to measure improvement of PV, NV, and other depressive symptoms (IDS_{22}). Both time and measure (PV, NV and other depressive symptoms) were repeated factors. Cohen's d effect sizes were presented based on model estimated means at week 12. PV, NV and other depressive symptom scores were converted into z-scores (mean zero, standard deviation of 1 at baseline) for graphical presentation. Participants with no post-baseline data or with baseline PV and/or NV symptom score of zero were not included in the analyses.

With respect to the association between PV and NV symptoms scores and baseline levels of immunomarkers, we log-transformed baseline concentrations of immunomarkers due to non-normal distributions. We then used Pearson's correlation coefficients to assess the relationship between PV and NV symptom scores and individual immunomarkers. Overall severity of MDD using IDS_{30}, and severity of non-PV non-NV symptoms (i.e. other MDD symptoms) using IDS_{22} were included in the analyses to assess if the correlations with PV and NV symptoms were specific of the PV and NV symptom dimensions. Partial Pearso's correlation coefficients were used to control for age, a variable with potential impact on concentrations of immunomarkers (Dowlati et al., 2010; Haapakoski et al., 2015). Since gender affects immune function (Afshan, Afzal, & Qureshi, 2012; Birur, Amrock, Shelton, & Li, 2017; Jha, Miller, Minhajuddin, & Trivedi, 2018), correlational analyses were repeated for males and females separately. Due to the exploratory nature of the analyses, no corrections for multiple comparisons were conducted.

3. Results

Operationalization of PV and NV symptoms

Based on the eight items extracted from the IDS-C_{30} (thought to best reflect the PV and NV systems), a confirmatory factor analysis was conducted which produced several goodness of fit statistics indicating the proposed division of items provided a good fit to the data, reinforcing that the items selected formed two distinct factors (Table 1). PV and NV symptoms had a modest positive correlation (Pearson's correlation coefficient of .224,

$p < .001$), as displayed in Supplemental Figure 1. Internal consistency as measured by Cronbach's alpha was 0.66 for PV and 0.43 for NV.

None of the remaining 22 IDS-C_{30} symptoms had a correlation above .45 with either PV or NV symptom scales. Pearson's correlation coefficient ranged between −.044 (distinct quality of mood) and .424 (depressed mood) for PV, and between −.057 (increased weight) and .286 (irritability) for NV (Supplemental Table 1). Consequently, no other items were added to either scale.

Sample demographics

For the 665 CO-MED participants, the mean scores for PV and NV scales were 8.7 (SD = 3.0) and 3.7 (SD = 1.8), respectively. The average age of the sample was 42.7 (SD = 13.0) and approximately two-thirds were female. The participants were moderately to severely depressed [mean score of 23.8 (SD = 4.8) for HAM-D_{17}, 15.8 (SD = 3.4) for QIDS-C_{16}, and 15.4 (SD = 4.3) for QIDS- SR_{16}]. The mean number of weeks in treatment was 9.9 (SD = 3.9), and the number of post-baseline visits was 5.3 (SD = 2.2). For full baseline characteristics, see Rush et al. (2011).

Regarding valence symptom scores, women had significantly higher PV scores. Age was positively correlated with PV scores and negatively correlated to NV scores. There was a negative correlation between PV and educational level (Table 2).

Associations with clinical features

PV and NV symptoms were substantially associated with different clinical features (Table 3).

With respect to the multivariate analyses, PV score was independently and positively associated with 1) *female gender* [B = 1.520, 95% CI (1.013, 1.937), t = 7.16, $p < .001$, standardized B = 0.240], 2) *older age* [B = .019, 95% CI (.004, .034), t = 2.53, $p = .012$, standardized B = 0.084], 3) *lower educational level* [B = −.121, 95% CI (−.186, −.056), t = −3.68, $p < .001$, standardized B = −0.122]; 4) *worse work and social adjustment* [B = .085, 95% CI (.060, .109), t = 6.79, $p < .001$, standardized B = 0.255] and 5) *worse cognitive and physical functioning* [B = .140, 95% CI (.103, .177), t = 7.46, $p < .001$, standardized B = 0.281]. Alcohol abuse, hypochondriasis, posttraumatic stress disorder, social phobia, somatoform disorder, and body mass index were excluded from the final model because they were not significant contributors. The model summary of the linear regression for PV symptom scores was $R^2 = .313$, degrees of freedom = 5, F = 57.77, $p < .001$.

NV symptom score was independently and positively associated with 1) *younger age* [B = −.012, 95% CI (−.022, −.002), t = −2.49, $p = .013$, standardized B = −0.002], 2) *generalized anxiety disorder* [B = .555, 95% CI (.213, .897), t = 3.19, $p = .002$, standardized B = 0.897], 3) *social phobia* [B = .504, 95% CI (.203, .806), t = 3.28, $p = .001$, standardized B = 0.806], 4) *worse work and social adjustment* [B = .022, 95% CI (.008, .037), t = 3.02, $p = .003$, standardized B = 0.037] and 5) *MDD-associated symptoms (CAST total score)* [B = .052, 95% CI (.038, .066), t = 7.15, $p < .001$, standardized B = 0.066].
The following variables were NOT independently associated with NV symptom scores:

agoraphobia, drug abuse, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, cognitive and physical functioning, number of psychiatric comorbidities, number of medical comorbidities, and body mass index. The model summary of the linear regression for NV scores was $R^2 = .219$, degrees of freedom = 5, F = 36.90, $p < .001$.

Response to antidepressants

NV symptoms were less responsive to antidepressants than PV symptoms (mean difference [PV-NV] = 0.469; standard error = 0.041; df = 2007; $p < .0001$) (Figure 1). PV ($p < .0001$) and NV ($p < .0001$) symptoms responded less to antidepressants than other MDD symptoms. There were no statistical differences between the three individual treatment arms in terms of improvement in PV or NV symptoms.

Associations with immunomarkers

At baseline, PV, but not NV, symptom scores showed statistically significant correlations with the level of three pro- and one anti-inflammatory immunomarkers (Table 4). Interestingly, most correlations between immunological factors (8/9) and PV symptom scores were positive, whereas most correlations between immunological factors (6/9) and NV symptoms scores were negative. In addition, the associations with levels of immunomarkers were stronger for PV symptoms than for overall MDD severity (IDS_{30}) or for other MDD symptoms (IDS_{22}). Overall, the correlations between inflammatory markers and PV and NV scores were numerically stronger in men than in women. Detection ranges and descriptions of the baseline levels of immunomarkers are displayed in Supplemental Table 2.

After controlling for age, the pro-inflammatory factors IFN-γ and, IL-6 showed the strongest associations with PV symptom scores (IFN-γ Pearson's partial correlation coefficient = .293, $p = .007$; IL-6 Pearson's partial correlation coefficient = .233, $p = .033$). In contrast, the pro-inflammatory IL-2 was the only immunomarker that had a significant correlation with NV symptom score (Pearson's correlation coefficient = −.267, $p = .014$).

4. Discussion

We found that we could operationalize a proxy for the concepts of PV and NV systems ~~function~~ in a concise, clinician-friendly manner by using selected symptoms that potentially reflect the function of each system. Results revealed that PV and NV symptom scores were substantially associated with different clinical features. PV symptoms were associated with female gender, older age, and higher cognitive and physical impairment, while NV symptoms were associated with younger age, more anxious comorbidities, and higher rates of other commonly associated non criterion symptoms. Further, NV symptoms were less responsive to antidepressants than PV symptoms, while both PV and NV symptoms responded less to antidepressants than other MDD symptoms (i.e. non-PV, non-NV symptoms). Finally, at baseline, PV (but not NV) symptom scores were significantly and positively correlated with several immunological factors (both pro-inflammatory and anti-inflammatory).

The emotional regulation and reward processes form the essence of the depressive syndrome and are reflected in the PV and NV system function as expressed symptomatically. Based on observable and reported symptoms, we developed a proxy for PV and NV systems (named PV and NV symptom scores) using a common depression questionnaire (IDS_{30}). These scores were associated with different clinical features, response to antidepressants and relationship with immunomarkers, suggesting that symptom scores might represent two systems that have different circuits and pathophysiology. This study is an initial attempt to conduct specific evaluations of PV and NV symptoms. In the future, assessment of PV and NV symptom scores in clinical practice may help treatment selection or prognostication.

NV symptoms were less responsive to antidepressants than PV symptoms - a finding that is consistent with previous findings that depression with significant NV symptoms, sometimes referred to as anxious depression, is associated with poorer response to antidepressants (Domschke et al., 2010; Fava et al., 2008). Anxious depression is usually defined as having a score of 7 or higher in the anxiety/somatization factor score of $HAM\text{-}D_{17}$, and is associated with lower remission rates when compared to non-anxious depression (Domschke et al., 2010; Fava et al., 2008). Although, PV was more responsive to antidepressants than NV, PV was less responsive to antidepressants than other MDD symptoms, which agrees with previous symptoms that anhedonia is a difficult-to-treat symptom (Lally et al., 2014; Papakostas & Ionescu, 2015). Similarly, Uher and colleagues (2012) analyzed remission rates as a function of severity of specific symptom dimensions in two large clinical trials. They found that worse severity in the interest-activity symptom dimension, which reflected “low interest, reduced activity, indecisiveness and lack of enjoyment”, predicted poor outcomes to treatment to monotherapy with three different antidepressants (citalopram, escitalopram and nortriptyline). Although different scales were used, the definition and operationalization of PV symptom dimension in our study was similar to their interest-activity dimension (Uher et al., 2012)., The use of dopaminergic and/or glutamatergic medications such as ketamine, memantine or pramipexol might better treat PV symptoms (Lally et al., 2014; Lemke, Brecht, Koester, Kraus, & Reichmann, 2005; Reus et al., 2012). Non-pharmacological interventions such as behavioral activation, CBT focused on positive affect, and exercise have showed positive results (Craske et al., 2019; Hopko, Lejuez, Ruggiero, & Eifert, 2003; Toups et al., 2017).

The correlation between baseline immunomarkers and PV (but not NV) symptom scores and multiple positive associations with baseline levels of pro- and anti-inflammatory factors is consistent with the notion that hedonic and motivational capacity may in part reflect immunological issues (De La Garza, 2005; Eisenberger et al., 2010; Felger et al., 2016). Primate studies found that exogenous administration of interferon-α, a pro-inflammatory cytokine, decreased dopamine release in areas largely associated with reward such as the striatum (Felger et al., 2013). Similarly, Eisenberger et al., (2010) found that administration of low doses of bacterial endotoxin was associated with decreased ventral striatum activity to reward cues in humans (Eisenberger et al., 2010). Felger and colleagues (2016) observed that systemic inflammation (reflected by concentration of CRP, IL-1β and other immunomarkers) was correlated with clinical anhedonia and lower connectivity between the striatum and the ventromedial prefrontal cortex, a key reward circuit (Felger et al., 2016). Taken together, these studies suggest that PV symptoms may be connected to inflammation

by impaired connectivity and decreased dopamine release induced by pro-inflammatory cytokines in reward-related circuits. Since PV symptoms had a significant relationship with immunological changes, the use of medications with anti-inflammatory properties may also specifically benefit those depressed patients with prominent PV symptoms. Some previous studies observed that medications that inhibit or antagonize inflammatory cytokines may help selected subjects with pro-inflammatory status (Raison et al., 2013; Savitz et al., 2018) or specific PV symptoms such as fatigue (Tyring et al., 2006).

PV and NV symptom scores were associated with distinct clinical and immunological features, although the scores were also modestly positively related to each other. PV and NV systems are relatively independent but have some degree of connection or common regulating structures. These systems seem to overlap in areas such as the amygdala and the striatum (Correia, McGrath, Lee, Graybiel, & Goosens, 2016; Janak & Tye, 2015). Another possible link between PV and NV systems is the common regulation by other brain structures such as the ventromedial pre-frontal cortex and the anterior cingulate cortex (Bogdan & Pizzagalli, 2006; Delgado et al., 2016; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015; Stevens, Hurley, & Taber, 2011). The ultimate result of the complex relationships between PV and NV systems are elaborated emotional responses and behaviors, and heterogeneous psychiatric disorders such as MDD (Hyman, 2007; Insel et al., 2010).

Limitations

First, the systems which underlie PV and NV are very complex and were derived from IDS_{30}, an instrument that was primarily developed to assessed overall depression severity, not specifically PV and NV symptom dimensions. Therefore, the clinical symptoms chosen to represent these systems may not fully capture all their functions. Second, the internal consistency for NV symptom score was relatively low. However, it must be considered that Cronbach's alpha is greatly influenced by the number of items and that, given that there are only 3 items in the scale, it is acceptable to use the NV symptoms score in this pilot study. Future research on PV and NV symptoms should develop more comprehensive measures. Third, this was a secondary analysis of a sample of opportunity from the CO-MED study that did not use emotional or biological measures such as functional neuroimaging, reward-tasks or electroencephalogram, which could further characterize PV and NV systems and correlate the symptom scores with actual system function. Despite our interesting findings, there is a clear need for further investigations on PV and NV symptoms using functional biological modalities. Fourth, the biomarkers component was part of an add-on study and thus only a subset of the CO-MED participants had blood available to evaluate immunomarkers. In addition, our conclusions are limited by not having some variables that can impact levels of immunomarkers such as smoking, fasting status, and time of the blood collection. Fifth, we had to exclude individuals with baseline symptom score of zero in a specific dimension (n = 17, 2.6%), and those who came just for the baseline visit (n = 31, 4.7%). Despite the total number of excluded participants was relatively small (n = 48, 7.2%), this might affect the generalizability of our findings. Finally, CO-MED was a trial of outpatients with recurrent or chronic nonpsychotic MDD, thus, additional caution is warranted in generalizing from this sample and replication of these findings

would strengthen its utility. Despite the limitations, this study has several strengths such as the conceptualization of a clinical proxy of PV and NV systems in a large clinical trial using a common depression questionnaire (IDS_{30}). The two dimensions obtained showed differential clinical and immunological associations, as well as distinct responsiveness to antidepressants.

Conclusions

PV and NV system function appears to be reflected in selected clinical symptoms that differentially relate to other clinical features, treatment outcomes and immunological function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

CO-MED study data may be requested through the NIMH Data Archive.

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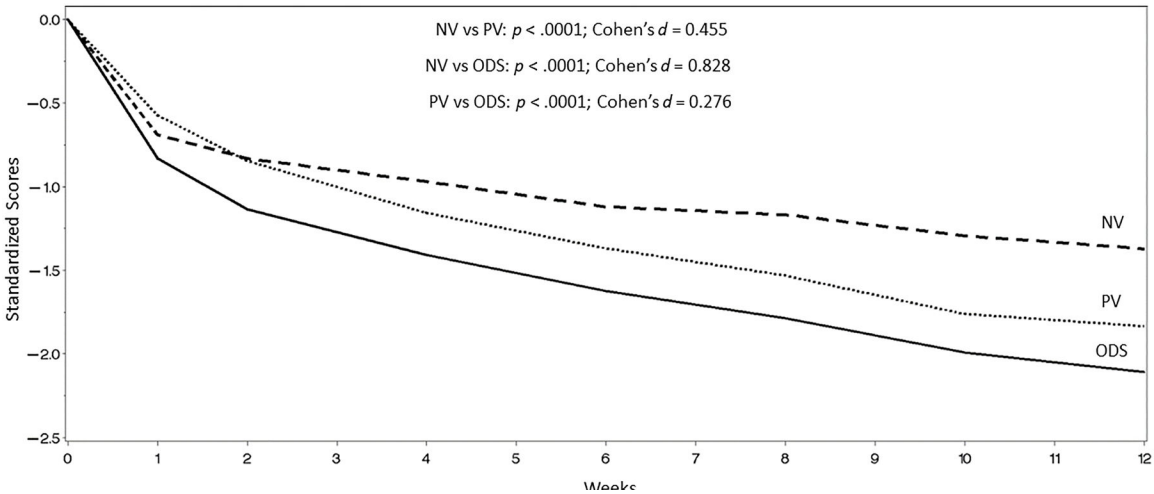

Figure 1: Improvement pf positive (PV) symptom scores, negative valence (NV) symptom score and other depressive symptoms(ODS) over 12 weeks, using a repeated measures mixed-effects model.

[a]Other symptoms consisted of the items of the Inventory of Depressive Symptomatology (IDS) that were not part of PV or NV symptom scores.

Table 1.

Confirmatory factor analysis of the items selected for the positive valence and negative valence symptom scores.

Index	Statistic	Interpretation[a]
Test of model fit	df=19, chi-square=27.8, p-value=0.087	No significant lack of fit
RMSEA (root mean square error of approximation)	0.026 95% CI (0.0, 0.046)	RMSEA between 0.05 and 0.02 indicates good fit
CFI (Comparative fit index)	.987	CFI between 0.95 and 0.99 indicates very good fit
TLI (Tucker-Lewis index)	.980	TLI between 0.95 and 0.99 indicates very good fit

[a]Longitudinal Structural Equation Modeling (Little, 2013).

Table 2.

Relationship between demographic/other depressive symptoms and positive/negative valence symptoms in individuals with major depressive disorder (MDD) (N=665).

Variables	POSITIVE VALENCE SYMPTOMS			NEGATIVE VALENCE SYMPTOMS		
	Severity of positive valence symptoms	**Statistical Significance**	**Statistical Significance**	**Severity of negative valence symptoms**	**Statistical significance**	**Statistical significance**
DEMOGRAPHICS						
Categorical variables	**Mean (SD[a])**	***p*** **[b]**	***Controlled p*** **[c]**	**Mean (SD[a])**	***p*** **[b]**	**Controlled *p*[c]**
Gender						
Male (n=213)	7.4 (3.0)	< .001	**< .001**	3.4 (1.8)	.002	.114
Female (n=452)	9.2 (2.8)			3.9 (1.8)		
Race						
Non-Black (n=485)	8.6 (2.9)	.605	.610	3.7 (1.8)	.845	.541
Black (n=180)	8.7 (3.2)			3.7 (1.8)		
Ethnicity						
Hispanic (n=101)	8.7 (3.2)	.939	.201	3.5 (1.7)	.257	.453
Non-Hispanic (n=564)	8.7 (2.9)			3.7 (1.8)		
Employed						
Yes (n=331)	8.5 (2.9)	.098	.979	3.7 (1.8)	.653	.970
No (n=334)	8.8 (3.0)			3.7 (1.8)		
Continuous variables	**Correlation coefficient**	***p***	**Controlled *p***	**Correlation coefficient**	***p***	**Controlled *p***
Age (years)	.022	.571	**.027** *d*	−.161	< .001	**< .001** *d*
Education (years) (n=642)	−.151	< .001	**< .001**	.000	.990	.639
Monthly household income (in dollars) (n=600)	−.070	.088	.314	−.065	.110	.491
OTHER DEPRESSIVE SYMPTOMS[e]						
Continuous variables	**Correlation coefficient**	***p***	**Controlled *p***	**Correlation coefficient**	***p***	**Controlled *p***
QIDS-C_{14}	.528	< .001	**< .001** *d*	.338	< .001	**< .001** *d*
IDS-C_{22}	.505	< .001	**< .001** *d*	.354	< .001	**< .001** *d*

[a] SD = standard deviation

[b] T-tests or ANOVA were used for categorical variables. Pearson's correlation coefficients were used for continuous variables

[c] Controlled *p* = scores controlled for age and overall MDD severity (QIDS-C$_{14}$)

[d] Age was controlled only for overall severity; other depressive symptoms were controlled only for age.

[e] Other depressive symptoms = MDD symptoms except PV and NV symptoms; Bold = statistically significant ($p < .05$) after controlling for age and overall severity.

Table 3.

Relationship between clinical features and positive/negative valence symptoms in individuals with major depressive disorder (MDD) (N=665).

Clinical Variables	POSITIVE VALENCE SYMPTOMS			NEGATIVE VALENCE SYMPTOMS		
	Severity of positive valence symptoms	Statistical Significance	Statistical Significance	Severity of negative valence symptoms	Statistical Significance	Statistical Significance
Categorical variables	**Mean (SD[a])**	***p*** **[b]**	**Controlled *p*[c]**	**Mean (SD[a])**	***p*** **[b]**	**Controlled *p*[c]**
Agoraphobia						
Yes (n=69)	9.3 (2.9)	.053	.814	4.5 (1.6)	< .001	**.004**
No (n=596)	8.6 (3.0)			3.6 (1.8)		
Alcohol abuse						
Yes (n=67)	7.9 (3.2)	.038	.072	3.9 (1.7)	.326	.280
No (n=597)	8.7 (2.9)			3.7 (1.8)		
Bulimia nervosa						
Yes (n=78)	8.6 (2.3)	.847	.330	4.1 (1.7)	.065	.311
No (n=587)	8.7 (3.0)			3.7 (1.8)		
Drug abuse						
Yes (n=35)	8.4 (3.4)	.604	.518	4.3 (1.9)	.052	.052
No (n=630)	8.7 (2.9)			3.7 (1.8)		
Generalized anxiety disorder						
Yes (n=131)	9.5 (2.9)	< .001	.290	4.8 (1.7)	< .001	**< .001**
No (n=534)	8.5 (3.0)			3.5 (1.7)		
Hypochondriasis						
Yes (n=29)	10.2 (2.7)	.003	.093	4.5 (2.4)	.092	.178
No (n=636)	8.6 (2.9)			3.7 (1.8)		
Obsessive-compulsive disorder						
Yes (n=79)	8.7 (3.3)	.857	.111	4.6 (1.9)	< .001	**< .001**
No (n=586)	8.6 (2.9)			3.6 (1.7)		
Panic disorder						
Yes (n=65)	9.4 (2.7)	.044	.993	4.8 (1.7)	< .001	**< .001**
No (n=600)	8.6 (3.0)			3.6 (1.8)		
Posttraumatic stress disorder						

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Clinical Variables	POSITIVE VALENCE SYMPTOMS			NEGATIVE VALENCE SYMPTOMS		
	Severity of positive valence symptoms	Statistical Significance	Statistical Significance	Severity of negative valence symptoms	Statistical Significance	Statistical Significance
Categorical variables	**Mean (SD[a])**	***p*[b]**	**Controlled *p*[c]**	**Mean (SD[a])**	***p*[b]**	**Controlled *p*[c]**
Yes (n=81)	8.8 (2.9)	.745	.073	4.6 (1.7)	< .001	**< .001**
No (n=584)	8.6 (3.0)			3.6 (1.8)		
Social Phobia						
Yes (n=178)	9.5 (2.7)	< .001	.083	4.6 (1.8)	< .001	**< .001**
No (n=487)	8.4 (3.0)			3.4 (1.7)		
Somatoform disorder						
Yes (n=21)	10.0 (2.2)	.028	**.025**	4.0 (2.0)	.532	.799
No (n=644)	8.6 (3.0)			3.7 (1.8)		
Continuous variables	**Correlation coefficient**	***P***	**Controlled *p***	**Correlation coefficient**	***p***	**Controlled *p***
Age at onset of first episode (years)	−.051	.189	.739	−.144	< .001	.560
Work and social adjustment	.408	< .001	**< .001**	.236	< .001	**.007**
Cognitive and physical functioning	.421	< .001	**< .001**	.222	< .001	**.029**
MDD-associated symptoms (CAST[d] total score)	.136	< .001	.334	.395	< .001	**< .001**
Number of psychiatric comorbidities	.115	.003	.850	.331	< .001	**< .001**
Number of medical comorbidities	.058	.132	.972	.024	.532	.089
Body mass index	.098	.012	**.031**	−.060	.120	.078

[a] SD = standard deviation

[b] T-tests were used for categorical variables. Pearson's correlation coefficients were used for continuous variables

[c] Controlled *p* = scores controlled for age and overall MDD severity ($QIDS\text{-}C_{14}$)

[d] Concise Associated Symptoms Tracking Scale; Bold = statistically significant ($p < .05$) after controlling for age overall severity.

Table 4.

Relationship between immunomarkers, and symptoms of major depressive disorder (MDD), N=166.

Variables	OVERALL SEVERITY (IDS_{30} TOTAL SCORE)		POSITIVE VALENCE SYMPTOMS		NEGATIVE VALENCE SYMPTOMS		OTHER MDD SYMPTOMS (IDS_{22})	
	r [a]	*p* [a]	*r* [a]	*p* [a]	*r* [a]	*p* [a]	*r* [a]	*p* [a]
ALL SUBJECTS (n=166)								
Primarily pro-inflammatory factors								
Log c reactive protein (CRP)	−.030	.784	−.044	.691	−.136	.219	.020	.859
Log interferon-gamma	.226	**.039**	.293	**.007**	.046	.676	.163	.140
Log interleukin 1 beta	.002	.986	.225	**.040**	−.009	.937	−.097	.379
Log interleukin 2 (n=94)	−.156	.157	.102	.354	−.267	**.014**	−.179	.104
Log interleukin 6 (n=160)	.011	.924	.233	**.033**	.005	.966	−.093	.400
Log interleukin 8 (n=165)	−.108	.329	.119	.280	−.017	.879	−.197	.072
Log TNF-alpha	.052	.640	.181	.100	−.035	.749	−.001	.996
Primarily anti-inflammatory factors								
Log interleukin 4	.072	.515	.224	**.041**	.109	.324	−.036	.743
Log interleukin 10 (n=127)	−.051	.644	.110	.321	−.040	.715	−.108	.328
MALES (n=49)								
Primarily pro-inflammatory factors								
Log c-reactive protein (CRP)	.050	.829	.122	.597	−.343	.128	.099	.670
Log interferon-gamma	.223	.332	.339	.133	.317	.162	.007	.975
Log interleukin 1 beta	−.123	.596	.300	.186	−.235	.305	−.258	.259
Log interleukin 2 (n=25)	−.199	.388	.270	.237	−.419	.059	−.286	.209
Log interleukin 6 (n=46)	.102	.659	.437	**.047**	−.054	.817	−.095	.682
Log interleukin 8	−.135	.559	.201	.383	−.408	.066	−.167	.468
Log TNF-alpha	.057	.806	.369	.100	−.238	.299	−.061	.791
Primarily anti-inflammatory factors								
Log interleukin 4	−.049	.834	.193	.401	.244	.287	−.244	.286
Log interleukin 10 (n=37)	−.036	.877	.273	.232	−.232	.312	−.131	.572
FEMALES (n=117)								

Variables	OVERALL SEVERITY (IDS_{30} TOTAL SCORE)		POSITIVE VALENCE SYMPTOMS		NEGATIVE VALENCE SYMPTOMS		OTHER MDD SYMPTOMS (IDS_{22})	
	r [a]	*p* [a]	*r* [a]	*p* [a]	*r* [a]	*p* [a]	*r* [a]	*p* [a]
Primarily pro-inflammatory factors								
Log c-reactive protein (CRP)	−.055	.671	−.108	.405	−.100	.441	.002	.991
Log interferon-gamma	.264	**.038**	.298	**.019**	−.046	.723	.253	**.048**
Log interleukin 1 beta	.053	.685	.214	.095	.044	.736	−.034	.795
Log interleukin 2 (n=69)	−.110	.394	.033	.802	−.227	.076	−.097	.454
Log interleukin 6 (n=114)	−.029	.825	.155	.228	−.008	.951	−.025	.845
Log interleukin 8 (n=116)	−.084	.516	.114	.376	.059	.647	−.186	.148
Log TNF-alpha	.067	.603	.083	.519	.010	.936	.054	.674
Primarily anti-inflammatory factors								
Log interleukin 4	.168	.192	.285	**.025**	.057	.660	.092	.475
Log interleukin 10 (n=90)	−.036	.781	.017	.894	.029	.826	−.067	.606

[a] Pearson's partial correlation coefficient and controlled *p* = scores controlled for age.

Bold = statistically significant ($p < .05$) after controlling for age. CRP measured in mg/L, other immunomarkers measured in pg/ml. IDS_{30} = Inventory of Depressive Symptomatology - Clinician Version. IDS_{22} = IDS_{30} excluding positive valence symptoms and negative valence symptoms items.

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