



Research paper

Parsing the heterogeneity of depression: An exploratory factor analysis across commonly used depression rating scales



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ABSTRACT

Background: Due to the heterogeneity of depressive symptoms—which can include depressed mood, anhedonia, negative cognitive biases, and altered activity levels—researchers often use a combination of depression rating scales to assess symptoms. This study sought to identify unidimensional constructs measured across rating scales for depression and to evaluate these constructs across clinical trials of a rapid-acting antidepressant (ketamine). **Methods:** Exploratory factor analysis (EFA) was conducted on baseline ratings from the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Snaith-Hamilton Pleasure Rating Scale (SHAPS). Inpatients with major depressive disorder ($n = 76$) or bipolar depression ($n = 43$) were participating in clinical ketamine trials. The trajectories of the resulting unidimensional scores were evaluated in 41 subjects with bipolar depression who participated in clinical ketamine trials.

Results: The best solution, which exhibited excellent fit to the data, comprised eight factors: *Depressed Mood, Tension, Negative Cognition, Impaired Sleep, Suicidal Thoughts, Reduced Appetite, Anhedonia, and Amotivation*. Various response patterns were observed across the clinical trial data, both in treatment effect (ketamine versus placebo) and in degree of placebo response, suggesting that use of these unidimensional constructs may reveal patterns not observed with traditional scoring of individual instruments.

Limitations: Limitations include: 1) small sample (and related inability to confirm measurement invariance); 2) absence of an independent sample for confirmation of factor structure; and 3) the treatment-resistant nature of the population, which may limit generalizability.

Conclusions: The empirical identification of unidimensional constructs creates more refined scores that may elucidate the connection between specific symptoms and underlying pathophysiology.

1. Introduction

Under DSM-5 criteria, an estimated 227 combinations of symptoms will lead to a diagnosis of a depressive episode. As a result, a wide range of individuals who meet criteria for depression may overlap on only a limited number of symptoms (Ostergaard et al., 2011; Zimmerman et al., 2015). Indeed, the heterogeneity inherent in the diagnosis of major depressive disorder (MDD) has been a consistent obstacle for identifying viable depression-specific biomarkers that could signal the presence of the disorder as well as predict and track treatment response

(Leuchter et al., 2010; Zarate et al., 2013).

Isolating specific clusters of the depressive syndrome with a particular biological signature may be an important step towards advancing translational research into depression and, concomitantly, developing novel therapeutics. However, the depression rating scales commonly used in clinical trials survey a variety of symptoms that reflect DSM criteria, which limits research in several key ways. For instance, such rating scales are useful in dichotomizing individuals into depressed vs. non-depressed samples, but provide little insight into specific symptom clusters that would lead to more homogeneous subgroups, as advocated

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by efforts such as the NIMH RDoC (Woody and Gibb, 2015). In this context, using unidimensional depressive symptom constructs could reduce variability in the data and increase the precision of attempts to connect specific symptoms with pathophysiology. However, it can be difficult to translate the multifaceted construct of depression across modalities—that is, from depressed patients to healthy control samples or to preclinical models. For example, a cross-method translational approach might first involve isolating a particular symptom construct (e.g., anhedonia or approach motivation) into specific neural circuits in patient samples, followed by an experimental paradigm to induce anhedonic symptoms in non-depressed healthy control participants, and finally into preclinical models of anhedonia in animal studies (Treadway and Zald, 2011). In a similarly translational fashion, findings from preclinical models of anhedonia could have implications for both healthy control and patient samples. However, this approach may be unnecessarily complicated by use of diffuse constructs like ‘depression’. Moreover, depression symptom domains may not have uniform response to treatment. For example, some symptom clusters may be particularly vulnerable to the placebo effect, some may exhibit differential response latency, and others still may not respond to a given intervention. These properties may have unexpected effects on the efficiency and precision of clinical trials, and it is possible—even likely—that researchers are unnecessarily handicapped by redundant use of multidimensional outcome measures.

This analysis sought to identify the unidimensional constructs measured by commonly used rating scales of depression and anhedonia, including the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Snaith-Hamilton Pleasure Rating Scale (SHAPS). Identifying such unidimensional constructs could then inform the identification of neurobiologically distinct subtypes (also known as biotypes) of depression. In particular, the inclusion of anhedonia and cognitive symptom-specific measures of depression across both clinician-administered and self-report assessments would allow the comprehensive examination of a range of experiences associated with depression. As an initial demonstration of these unidimensional constructs, and in order to assess whether the identified constructs have neurobiological relevance, we examined how these symptoms change in response to a rapid-acting pharmacologic intervention (the glutamatergic modulator ketamine) compared with traditional measures of depression. The literature on depressive biotypes is growing rapidly—in part related to imaging connectivity analyses (Drysdale et al., 2017; Williams, 2017) and the ongoing search for central or peripheral biomarkers (Lamers et al., 2013)—and we believe that careful parcellation of depressive symptoms and behaviors is critical to ensuring that these biotypes have clinical relevance and significance.

2. Methods

2.1. Participants

One hundred nineteen currently depressed patients (61 male, 58 female; aged 21–66, mean age = 45.28 years, SD = 12.45) were recruited from inpatient studies conducted at the National Institute of Mental Health, National Institutes of Health (NIMH-NIH), Bethesda, MD, USA. The patient sample comprised 76 subjects diagnosed with major depressive disorder (MDD) and 43 diagnosed with bipolar depression (either I or II); the presence of psychotic features was an exclusion criterion for both diagnoses. All patients participated in trials on the same research unit and were assessed and treated by the same clinical and research staff. All trials examined the use of ketamine as a rapid-acting antidepressant; results have been previously published (Diazgranados et al., 2010b; Ibrahim et al., 2012; Zarate et al., 2012, 2006).

Participants were initially screened and evaluated for eligibility for research participation, which included an initial MADRS score ≥ 20 or

a HAM-D score ≥ 18 across all trials. Once at the NIH, diagnosis was established using the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV (First et al., 2002)) and corroborated by a team of clinicians using all available information. All subjects were in good physical health as determined by medical history, physical examination, and laboratory tests. Exclusion criteria included pregnancy, nursing, or illicit comorbid substance abuse in the previous three months. Written informed consent was obtained from all participants, and the NIH combined Neuroscience Institute Review Board approved the study.

Across all trials, the co-occurrence of Axis I anxiety disorders was permitted if it was not the primary focus of treatment within the past 12-month period. At hospital admission, all subjects were currently experiencing a major depressive episode lasting at least four weeks. Once admitted and where necessary to comply with individual protocols, subjects were tapered off of their existing medications and underwent a two-week drug-free period (five weeks for fluoxetine, three weeks for aripiprazole) before study baseline. All patients diagnosed with bipolar depression were maintained on a therapeutic dose of either lithium (serum lithium, 0.6–1.2 mEq l⁻¹) or valproic acid (50–125 $\mu\text{g ml}^{-1}$) for four weeks without exhibiting an antidepressant response to the prescribed medication. No other psychotropic medication or psychotherapy was permitted during the drug-free period prior to study baseline or throughout the study. All subjects, with one exception, were considered treatment-resistant, defined as having failed to respond at least one adequate treatment trial, as determined by the Antidepressant Treatment History Form (Sackeim, 2001).

2.2. Design

Details regarding study designs can be found elsewhere (Diazgranados et al., 2010b; Ibrahim et al., 2012; Zarate et al., 2012, 2006). Briefly, patients were administered psychiatric scales in the morning, approximately one hour before beginning their first infusion (regardless of whether the study was open-label or placebo-controlled). This pre-infusion baseline was a time where patients had been medication-free for at least two weeks, with the exception of those patients with bipolar depression who were maintained on lithium or valproate. Ketamine was administered intravenously at 0.5 mg/kg; in the placebo-controlled studies, saline infusions were used as the control condition. The psychiatric rating scales were re-administered to patients at 40, 80, 120, and 230 min post-infusion and at Days 1, 2, and 3.

From the larger patient group of 119 depressed participants, longitudinal data from 41 subjects with bipolar depression were used to assess the unidimensional scores in clinical trials. Most of the bipolar depression patients (n = 33) had participated in one of two randomized, placebo-controlled, crossover trials of ketamine (an initial trial and a replication) (Diazgranados et al., 2010b; Zarate et al., 2012). The remaining eight participants were drawn from ongoing biomarker studies. These studies were specifically selected for use in this preliminary analysis due to the uniformity of diagnosis, use of all relevant measures, and similarity of research design; it should be noted that for the eight participants drawn from our ongoing biomarker studies, identical methods were used regarding recruitment procedures, inclusion/exclusion criteria, and study protocols. Patient demographics and treatment response did not differ across sources (see Supplementary Table 1).

2.3. Measures

The BDI (Beck et al., 1961) is a 21-item self-reported measure of depression severity. Items are framed as aspects of depressive symptomatology such as “Sadness”. Answers are measured on a 0–3 scale, with higher scores indicating increased severity of depressive symptoms (e.g., “I do not feel sad” to “I am so sad or unhappy I can’t stand it”). The BDI has high internal reliability (Beck et al., 1961) and concurrent

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