



Cross-diagnostic Prediction of Dimensional Psychiatric Phenotypes in Anorexia Nervosa and Body Dysmorphic Disorder Using Multimodal Neuroimaging and Psychometric Data

Jamie D. Feusner^{1,2(✉)}, Wesley T. Kerr^{1,2,3}, Teena D. Moody^{1,2},
Aifeng F. Zhang⁴, Mark S. Cohen^{1,2}, Alex D. Leow^{4,5},
Michael A. Strober^{1,2}, and Don A. Vaughn^{1,6}

¹ Semel Institute for Neuroscience and Human Behavior,
University of California, Los Angeles, CA, USA
JFeusner@mednet.ucla.edu

² David Geffen School of Medicine, University of California,
Los Angeles, CA, USA

³ Department of Internal Medicine, Eisenhower Health,
Rancho Mirage, CA, USA

⁴ Department of Psychiatry, University of Illinois, Chicago, IL, USA

⁵ Department of Bioengineering, University of Illinois, Chicago, IL, USA

⁶ Department of Psychology, Santa Clara University, Santa Clara, CA, USA

Abstract. Anorexia nervosa (AN) and body dysmorphic disorder (BDD) share several phenomenological features including distorted perception of appearance, obsessions/compulsions, and limited insight. They also show partially overlapping patterns of brain activation, white matter connectivity, and electrophysiological responses. These markers have also shown associations with symptom severity within each disorder. We aimed to determine: (a) if, cross-diagnostically, neural activity and connectivity predict dimensional clinical phenotypes, and (b) the relative contribution of multimodal markers to these predictions beyond demographics and psychometrics, in a multivariate context. We used functional magnetic resonance imaging (fMRI) data from a visual task, graph theory metrics of white matter connectivity from diffusor tensor imaging, anxiety and depression psychometric scores, and demographics to predict dimensional phenotypes of insight and obsession/compulsions across a sample of unmedicated adults with BDD ($n = 29$) and weight-restored AN ($n = 24$). The multivariate model that included fMRI and white matter connectivity data performed significantly better in predicting both insight and obsessions/compulsions than a model only including demographics and psychometrics. These results demonstrate the utility of neurobiologically-based markers to predict important clinical phenotypes. The findings also contribute to understanding potential cross-diagnostic substrates for these phenotypes in these related but nosologically discrete disorders.

Keywords: fMRI · DTI · Insight · Obsessions · Compulsions
Multivariate

1 Introduction

Anorexia nervosa (AN) and body dysmorphic disorder (BDD) are psychiatric disorders with a high risk of morbidity and mortality [1]. Core symptoms of AN include reduced caloric intake, low body weight, fear of becoming fat, and disturbed experience of one's body or weight; in BDD these include preoccupation with perceived defects in appearance and repetitive behaviors to check, fix, change, or hide aspects of their appearance [1].

AN and BDD are categorized as an eating disorder and as an obsessive-compulsive related disorder, respectively, yet they share phenomenological features such as distorted perception of appearance, poor insight [2, 3], and obsessive and compulsive symptoms [4]. Of those with AN, 25–39% are diagnosed with lifetime BDD; 32% of those with BDD will have a lifetime eating disorder [5, 6]. Additionally, 30% of those with BDD have weight-related appearance concerns (e.g. their cheeks or thighs being too fat) [7]. Similarities have raised the question of whether one disorder should be considered a subtype of the other, or that they share pathological features [8].

The few studies that have directly compared the neurobiology of AN and BDD demonstrate overlapping and distinct patterns of neural activity and connectivity [9, 10]. Several of these studies have also examined associations between neural markers and clinical symptoms. N170 ERP amplitude correlated with insight in BDD but not in AN [10]. Insight was correlated with a graph theory network measure, normalized path length (NPL), in white matter in AN but not in BDD [3, 10]. Studies in BDD have shown associations between obsessions and compulsions and activation in prefrontal, striatal, and visual regions [11]; with connectivity in the orbitofrontal cortex [12]; and with whole-brain white matter connectivity (global efficiency) [13]. Insight in BDD is associated with regional white matter diffusion in tracts relevant to visual processing [14].

Whether common phenotypic symptom profiles are associated with underlying brain activation patterns and white matter structural properties remains unexplored. This is relevant, as psychiatric disorders once assumed to be causally independent have been found to have common genetic variant risks [15]. Such relationships could inform underlying shared or unique neurobiological and brain-behavior relationships contributing to dimensional phenotypes. Accordingly, a goal of this study was to determine if, cross-diagnostically, neural activity and connectivity patterns predict dimensional phenotypes. Potential clinical value of this would be at the cost of obtaining neuroimaging markers, which is not part of standard clinical practice; thus, a second goal was to determine the relative predictive contribution of imaging markers beyond demographic and psychometric data. We hypothesized that neural activity and connectivity patterns would significantly predict insight and obsession/compulsion phenotypes across AN and BDD, and would provide additional significant predictive value beyond demographics and psychometrics, in a multivariate context.

2 Methods

2.1 Participants

Fifty-three individuals participated, between the ages of 14 and 38. Twenty-nine met Diagnostic and Statistical Manual (DSM-IV) [16] criteria for BDD, and 24 for AN, aside from being weight-restored ($\text{BMI} \geq 18.5$) to avoid confounds of starvation state (Table 1).

Table 1. Demographics. Errors are standard deviation.

Variable	AN	BDD	P
Number of participants	24	29	N/A
Age (years)	21 ± 5	23 ± 5	0.17
Sex: female	23/24 (96%)	26/29 (90%)	0.62
Illness duration (log months)	3.7 ± 1.2	4.6 ± 0.7	0.01
BMI	20 ± 2	22 ± 3	0.02
Lowest lifetime BMI	16 ± 2	N/A	N/A

Participants were free from psychoactive medications for at least 8 weeks. For detailed inclusion and exclusion criteria please see our previous publications [3, 9, 10].

2.2 Psychometrics

All received clinician-rated scales: the Brown Assessment of Beliefs Scale (BABS) [17] (higher scores indicate worse insight), the Hamilton Anxiety Rating Scale (HAMA) [18], and the Montgomery-Asberg Depression Scale (MADRS) [19]. To measure obsession and compulsions, the BDD group received the BDD version of the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS) [20] and the AN group received a version of the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS) [21] modified to match the BDD-YBOCS on total numbers of items and a single avoidance and a single insight item. To generate a single regression for predicting obsessions/compulsions, we aggregated data from both groups into one outcome variable, the “YBC/BDD-YBOCS.” HAMA and MADRS were correlated ($r = 0.78$) so we collapsed them into one metric, “HAMADRS,” by using the first principal component, which explained 82% of the variance.

2.3 Overview and Rationale of Variable Selection

A goal was to create a prediction model to understand multivariate relationships between insight and obsessions/compulsions across AN and BDD, with functional and structural brain measures, psychometrics, and demographics. We used structural (DTI) and functional (fMRI) data, anxiety and depression (HAMADRS), insight

(BABS), and obsessions/compulsions (BDD-YBOCS and modified YBC-EDS) ratings. From DTI, we used NPL to provide a summarized metric of global white matter network connectivity. We included fMRI data from a task of viewing images of bodies, and faces (visual stimuli that are relevant to participants' appearance concerns) and houses (which are unrelated to appearance concerns).

2.4 fMRI Data

We collected fMRI data on a 3T scanner as participants matched high, normal, and low spatial-frequency images of others' bodies, faces, and houses, as previously described [9, 22]. To derive a signal metric per network, we extracted network coherence values from three networks of interest: primary visual (PV), higher order visual (HV), and salience networks [22]. We collected 64 gradient direction diffusion-weighted images, with $b = 1000 \text{ s/mm}^2$ and one minimally diffusion-weighted scan. Graph theory metrics were calculated from deterministic tractography-derived connectivity matrices using Freesurfer (Martinos Center for Biomedical Imaging, USA) parcellation of T1 images, as previously described [3]. Shortest path length between each pair of nodes was averaged over all nodes to obtain the characteristic path length (CPL). The normalized path length (NPL) is the ratio of observed CPL to the CPL of an identically sized but randomly connected network [23].

2.5 Missing Data Imputation with Multiple Imputation

We addressed missing data using multiple imputation [24, 25]. We had data for 100% of participants for HAMA/MADRS, 85% of the BABS, 100% of DTI, and 68% of fMRI. We conservatively assumed that data were missing completely at random, namely, unrelated to diagnosis and severity of illness. We used a transformed-linear multivariate model to estimate the covariance of variables, with illness duration modeled as log-linear. We chose this imputation strategy as there was insufficient evidence to suggest that non-linear trends existed, and insufficient data to reliably estimate nonlinear terms within each model. Missing values were imputed 20 independent times based on posterior probabilities of the estimate of the missing data using this multivariate transformed-linear model. The initial values were cold-deck imputed and, to improve exploration of the whole parameter space and reduce tendencies to fall into local minima due to the relatively small dataset, the estimated covariance was multiplied by an exponentially decaying dispersion term with magnitude of 1% after 100 iterations. Each imputation consisted of 400 iterations, although most imputed datasets converged within 200 iterations.

2.6 Statistical Modeling

Linear associations of demographic (age, sex, BMI), clinical variables (AN or BDD diagnosis, the log of illness duration), psychometric scores (HAMADRS, and BABS for the YBC/BDD-YBOCS model), and MRI features (NPL; salience, HV, PV coherence values) with the cross-diagnostic clinical phenotypes of BABS and YBC/BDD-YBOCS (separately) were evaluated using multivariate linear regression. Log-likelihood tests evaluated if including MRI-based features significantly improved the model as compared to only demographic and clinical variables; or demographic, clinical variables and psychometric scores. Primary predicted outcomes were BABS and YBC/BDD-YBOCS; imputation and regression modeling of each were performed separately.

3 Results

3.1 BABS

Model predictions using just demographic variables were significantly different from a constant model (deviance difference 280.7, $df = 4$, $p = 10^{-59}$). MRI-based features significantly improved the model as compared to just demographic and clinical variables (deviance difference 89.1, $df = 5$, $p = 10^{-17}$); and a model including demographic, clinical variables and HAMADRS (deviance difference 83.5, $df = 4$, $p = 10^{-17}$, Fig. 1A). The only factor that trended towards individually significant association was group; the BDD group having a 3.8 higher score than AN (SE 2.2, $p = 0.08$, Fig. 1B).

3.2 YBC/BDD-YBOCS

Model predictions using just demographic variables significantly differed from a constant model (deviance difference 798.7, $df = 4$, $p = 10^{-171}$). MRI-based features significantly improved the model compared to including just demographic and clinical variables (deviance difference 550.5, $df = 6$, $p = 10^{-115}$); and a model including demographic, clinical variables, and psychometric scores (deviance difference 233.4, $df = 4$, $p = 10^{-49}$, Fig. 1C). The only factors that had significant individual associations were group, with the BDD group having a 8.2 higher score (SE 2.7, $p = 0.003$, Fig. 1D) and HAMADRS with a unit effect of 6.4 (SE 2.5, $p = 0.01$).

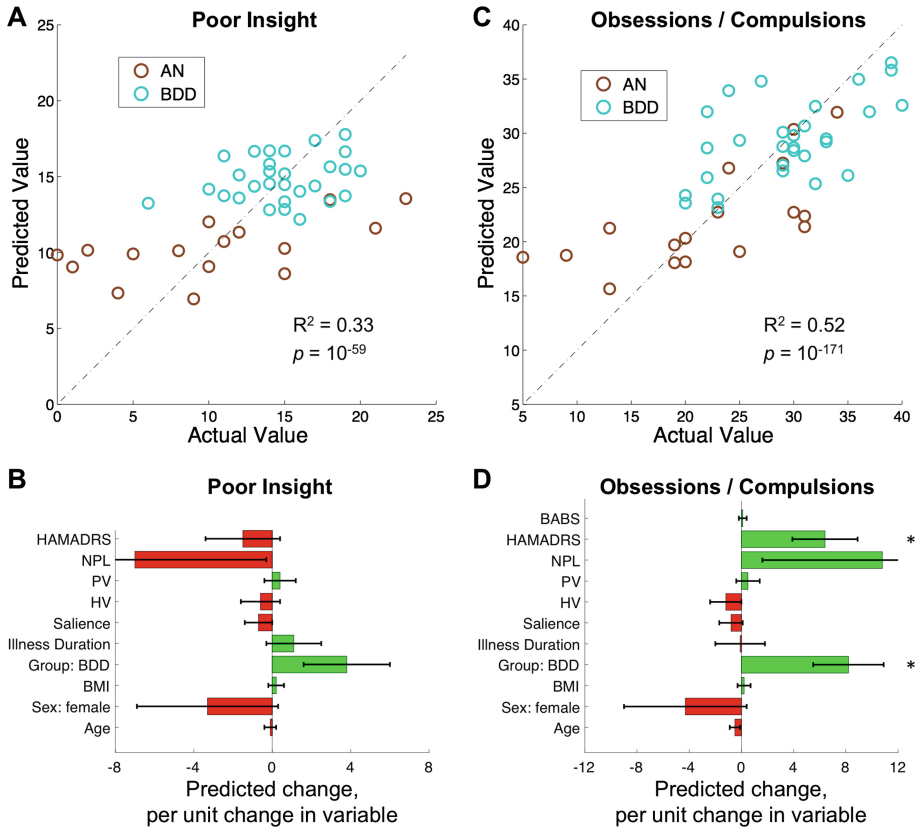


Fig. 1. Model performance and features. A. Performance of the BABS model in predicting participants' observed values. B. Feature weights and errors from the BABS model. C. Performance of the YBC/BDD-YBOCS model in predicting participants' observed values. D. Feature weights and errors from the YBC/BDD-YBOCS model. An asterisk signifies $p < 0.05$.

4 Discussion and Conclusions

A multivariate model that included brain structure and function, psychometrics, and demographics demonstrated significant predictions for both insight and obsessions/compulsions. Moreover, neuroimaging-derived data significantly improved the predictive ability of the model beyond the psychometric and demographic data.

Results suggest that brain structure and function, anxiety and depression, and demographic variables contribute to poor insight across AN and BDD. NPL appeared to contribute more, individually, to predicting insight and obsessions/compulsions than did activation in visual and salience networks. However, inherent to this multivariate analysis is the possibility of complex relationships between variables that do not lend themselves to being disentangled and interpreted in terms of contributions of individual parts.

Models with neurobiological variables were better predictors over the reduced models. This provides early promise that neuroimaging markers might provide clinical utility for predicting dimensional severity of phenotypes across disorders, longitudinally. This requires verification in larger, and longitudinal, studies and those that target specific patient cohorts such as those in early stages of illness or at-risk, to prove pragmatic utility. This is important due to additional costs with neuroimaging.

The sample size limited our ability to include other potentially informative neurobiological and demographic variables. Other statistical modeling approaches—such as training on broader sets of whole-brain activation and connectivity features in a more data-driven manner—could also be applied with larger samples and may improve predictive performance. We had missing data, although we mitigated this by using multiple imputation. We modified the YBC to match the BDD-YBOCS, although the validity and reliability of this modified version has not been tested.

Results shed light on possible shared neurobiological contributors to symptoms in AN and BDD, including white matter network organization indexing long-distance efficiency of brain connections and connectivity within higher- and lower-order visual and salience networks. A tentative model is one in which the combination of specific patterns of visual processing of symptom-related stimuli, combined with specific patterns of white matter network “scaffolding” for how this information integrates across the brain, in the context of anxiety/depression and specific demographics, contributes to worse insight and obsession/compulsion symptoms. A strength of the current analysis is that, as opposed to previous univariate analyses, the functional and structural neurobiological contributors are integrated in a more realistically complex context of variable symptom severity and clinical variables. Our dimensional approach also circumvents limitations of categorical diagnostic categories [26]. This study provides early proof-of-concept for multimodal neurobiological, psychometric, and demographic variables to understand contributors to cross-diagnostic phenotypes and potentially to predict dimensional symptom profiles.

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