Commentary

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Regression Models for Characterizing Categorical-Dimensional Brain-Behavior Relationships in Clinical Populations

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Clinical functional magnetic resonance imaging studies have traditionally used either categorical analyses or dimensional analyses to characterize brain-behavior relationships related to clinical symptomatology. Categorical analyses identify group differences in brain function according to discrete categories—for example, contrasting individuals with and without a diagnosis of attention-deficit/hyperactivity disorder (ADHD). Dimensional analyses characterize the relationship between brain function and individual symptomatology along a continuum of symptom severity regardless of diagnosis. For example, even though an individual may not have an official diagnosis of ADHD, he or she might still exhibit some behavioral symptoms of the condition. Recently, investigations have begun to examine both categorical and dimensional relationships within the same analytic framework in conditions such as ADHD (1,2) and autism spectrum disorder (3). These categorical-dimensional analyses have generally been assessed using a linear regression model using categorical and dimensional predictors together within a single model or separately using different models. However, such approaches can be problematic because categorical and dimensional predictors from the same clinical population are often highly collinear. For example, individuals with an ADHD diagnosis should have significantly higher scores on assessments of ADHD symptoms than individuals without an ADHD diagnosis. Because of the collinearity between such predictors, the sensitivity of a regression model with both a categorical and a dimensional predictor decreases because variance common to each predictor is controlled for and not modeled in such an approach. Thus, only the unique variance related to a specific predictor of interest is represented in the results. However, if categorical and dimensional predictors are assessed in separate regression models, the overlapping variance related to each predictor is ignored. Thus, effects caused by a nonmodeled predictor cannot be ruled out. In other words, a model with only a categorical predictor may produce effects that could be attributed to the dimensional predictor that was not included, and vice versa. The field would benefit from an analysis that is able to reconcile the tradeoffs between full variance modeling and unique variance modeling when investigating categorical–dimensional relationships.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Pruim *et al.* (4) present a novel and promising two-step regression framework for reconciling the problems of full variance and unique variance modeling within a categorical-dimensional framework. This allowed Pruim *et al.* (4) to identify overlapping and unique relationships related to categorical and dimensional predictors. Pruim *et al.* (4) first identified 14 canonical large-scale neural networks within a small independent sample of typical individuals (n = 46) using an independent component analysis. Next, individual-level spatial maps for those 14 networks representing the connectivity strength of each voxel to the rest of the network were reconstructed in the main sample (n = 409; 17.5 ± 3.3 years) using FSL's dual regression approach (5). These subject-level spatial connectivity strength maps were then used as dependent variables within a two-step regression framework involving a full variance model followed by a unique variance model.

In the first step, a full variance regression model assessed the relationship between three predictors of interest (ADHD diagnosis, inattention symptoms, and hyperactivity/impulsivity symptoms) and functional connectivity (FC) strength. In order to isolate the full variance of a given predictor, three separate regression models were run. First, the predictor of interest was regressed out of the other two predictors. Second, the residuals of the remaining two predictors were entered into the regression model. This ensured that the predictor of interest would now represent the shared variance originally represented in the other two predictors before residualization. This identified differences in functional connections related to full variance modeling of each of the three predictors. Nonparametric permutation testing identified 27 spatial clusters capturing the full variance of each predictor separately that Pruim *et al.* (4) referred to as "FC markers."

In the second step, a unique variance regression model then used the subject-level mean voxelwise values from each FC marker, called FC marker scores, to isolate the unique variance related to each predictor. Similar to step 1, three regression models were run in step 2. First, the variance from the two other predictors were first regressed out of the predictor of interest. Note that this is the opposite of step 1, where the predictor of interest was regressed out of the remaining two predictors. Second, the remaining residuals from the predictor of interest were then entered in a regression model with the other two predictors of interest. This resulted in only the unique variance for each predictor of interest being assessed within each regression model.

The results of Pruim *et al.* (4) demonstrated that categorical differences due to ADHD diagnosis were mainly found within the posterior cingulate and prefrontal cortex within the default mode network. Dimensional differences due to inattention symptom severity were found mainly in the middle prefrontal gyrus of the default mode network; hyperactivity/impulsivity symptoms were found mainly within sensorimotor, visual, and

SEE CORRESPONDING ARTICLE ON PAGE 472

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cerebellar networks. Finally, both categorical and dimensional effects were found mainly in the anterior cingulate related to the salience network and in the striatum. In addition, analyses linked FC marker scores to neurocognitive measures related to inhibition, visuospatial working memory, reward sensitivity, and reaction time variability, further demonstrating the utility of the approach. Thus, the two-step regression model was able to make a significant contribution to understanding ADHD neurobiology by identifying overlapping and unique categorical and dimensional effects for the first time.

The two-step categorical-dimensional regression approach has the ability to inform clinical resting-state functional magnetic resonance imaging investigations using other measures of brain function, such as brain signal variability (2), dynamic FC (6), and local connectivity (e.g., regional homogeneity) (7). For example, we recently demonstrated that brain signal variability of the resting-state blood oxygen level–dependent signal within the prefrontal cortex was positively correlated with Conners ADHD Index and ADHD inattentive symptom severity across individuals with and without a diagnosis of ADHD (2). This dimensional effect was present in the absence of any categorical effect of diagnosis. However, our approach used separate regression models to investigate categorical and dimensional effects. As Pruim *et al.* (4) point out, this approach would not rule out the possibility that categorical differences were contributing to our reported dimensional effect. Application of the two-step regression model would afford us the opportunity to more closely examine these types of issues and rule out the possibility that shared variance from categorical and dimensional predictors was driving the results. Thus, the two-step regression approach introduced by Pruim *et al.* (4) will inform various investigations examining relationships between neurobiology and clinical symptomatology regardless of brain function measure.

The two-step regression approach introduced by Pruim *et al.* (4) also follows on a recent publication investigating categorical-dimensional relationships in autism spectrum disorder. Elton *et al.* (3) used linear hierarchical regression to account for nested effects of scanner site, a mean connectivity predictor to account for global connectivity effects (e.g., head motion and respiration), and a predictor representing categorical by dimensional interactions. Although Pruim *et al.* (4) did not use subjects from different scanner sites, the movement toward large, publicly available databases related to clinical etiology is becoming increasing popular as a means to investigate clinical neurobiology. Thus, nested models accounting for scanner site variation will become increasingly important as new larger, publicly available databases combining data from different institutions become available. In addition, although Pruim *et al.* (4) did use ICA-AROMA (8) to remove nonneuronal artifacts, previous research has shown that global connectivity artifacts may still persist (9), making the use of a global predictor in a regression model an interesting alternative to global signal regression owing to the controversy over its application (10). Finally, using an interaction term to investigate categorical-dimensional relationships is a slightly different approach from the two-step regression model by Pruim *et al.* (4) because it assesses the interaction of predictor slopes as opposed to characterizing individual slopes while controlling or not controlling for other predictors. Future research is needed to understand how various combinations of different regression approaches may characterize different aspects of categorical-dimensional relationships in clinical populations.

In conclusion, the studies by Pruim *et al.* (4) and Elton *et al.* (3) make important contributions to investigations interested in categorical-dimensional relationships in clinical populations. Future researchers will most likely need to consider incorporating aspects from both the regression models used by Pruim *et al.* (4) and Elton *et al.* (3) to better characterize overlapping and unique attributes related to categorical and dimensional differences. These newly introduced regression approaches applied to clinical functional magnetic resonance imaging studies that investigate brain-behavior relationships afford the opportunity to make promising new neurobiological discoveries in clinical populations such as ADHD and autism spectrum disorder.

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