Correspondence

The Value of Hyperalignment to Unpack Neural Heterogeneity in the Precision Psychiatry Movement

To the Editor:

In the past decade, there has been a movement in psychiatry to diverge from classical DSM diagnoses toward dimensional symptom profiles (1). This change coincided with an observation that while some symptoms appear specific to a given disorder, others are observed across clusters of related disorders (2). While this shift has advanced our understanding of structural models of clinical symptoms (3), a gap exists in relating these models to corresponding functional brain organization at the individual subject level (4). This creates a discrepancy between increasingly specific symptom profiles and the methods that we use to define correspondingly specific functional circuitry underlying psychopathology. Fortunately, current work in other domains of cognitive neuroscience has developed methods to capitalize on individual differences in functional magnetic resonance imaging (fMRI) in an attempt to address intersubject heterogeneity in neural data. One of these methods, hyperalignment (5), may be particularly suited to the task of mapping dimensional symptom profiles onto changes in neural circuitry. Here, we contrast hyperalignment to other analysis methods to point out some key differences that could be crucial to improving our understanding of how structural symptom models relate to neural mechanisms at the individual subject level.

A common neuroimaging approach to explore group differences is region-of-interest analysis. In a clinical context this approach involves the comparison of average signal in regions of interest between clinical populations and normative control subjects. The problem here is an assumption that all voxels within a region of interest will activate in the same way across individuals, and such approaches have recently been associated with low reliability when applied to task-based fMRI (6). In other words, these approaches average meaningful patterns of neural activity across voxels and blur task-related signal, which artificially reduces effect sizes. In contrast, multivariate methods appear to be more sensitive to task-related brain states and account for individual differences at the voxel level (7). While these methods provide a needed boost in our ability to identify reliable task-based brain states, heterogeneity in the structural organization of voxels across individuals continues to cloud neural information encoded in this functional topography.

To address this problem, hyperalignment leverages the idea that, within an individual, distinct neural populations are reliably active but spatially distinct. This is done by extracting reliable locations (voxels) from each subject that consistently respond to a specific stimulus (5). One example of this work focused on patterns of brain activation specific to face and object recognition in the ventral temporal cortex (5). In this study, an initial extraction of reliable voxels from each subject reveals an idiosyncratic topography of neural representations related to each of the presented stimuli. While standard methods might assume that each location (voxel) corresponds with the same functional information across people, hyperalignment works to maximize the correspondence of these locations across subjects. This first involves representing brain data in a high dimensional space. These representations are then aligned across subjects through a Procrustean transformation. This rotates each subject's functional data into a shared common space and acts as a form of universal translator in which correspondence between individual specific patterns of functional data is maximized.

This improvement in alignment across subjects has led to large increases in classification of task-based fMRI data (5,8), which was previously hampered by variability in a subject's spatial topography. Hyperaligned data have also been used to classify complex stimuli using prediction-based analysis (9) and to project activation back onto individual brains to illuminate underlying mechanisms related to perceptual and cognitive function (5). This work highlights two strengths of hyperalignment. First, maximizing correspondence between individual subject's brain data highlights common neural circuits shared among subjects within a sample (5). This allows for the identification of shared neural activation across subjects despite slight topographical differences in individual subjects. Second, by aligning subjects based on their commonalities, brain activation specific to a single person or to a relevant group may be more easily identified. These strengths have critical implications for clinical neuroscience.

Consider a hypothetical application that evaluates risk for developing mood and anxiety disorders in youth. To determine risk, researchers collect multiple longitudinal time points of a reward task. However, the underlying functional neuroanatomy of reward may vary across individuals (10), decreasing effects and obscuring patterns related to mood and anxiety symptoms. Hyperalignment can be applied to improve correspondence between a subject's brain data, illuminating commonalities in reward responses (increasing effect sizes) as well as differences in the local weighting of reward related features across participants. It is also possible that clinically relevant patterns of functional data may be identified that fail to be hyperaligned between neurotypical and depressed youths. This could reveal underlying neurobiology unique to specific depressive symptoms or may identify brain features that underlie risk for future onset of depressive symptoms. This principle may also prove effective in breaking down issues related to the comorbidity of clinical symptoms. The alignment of commonalities across subjects diagnosed with anxiety and depression would illuminate brain regions that predict psychopathology more generally, while regions that remain distinct between clinical groups following hyperalignment would highlight neural circuits specific to that subtype of clinical disorder. Techniques such as hyperalignment will be crucial in identifying fine-grained differences at the core of these kinds of questions.

The mapping of specific symptoms to specific neural mechanisms is central to the precision psychiatry movement.

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Current neuroimaging research has been hampered by the issue of addressing intersubject neural heterogeneity while defining group level constructs that help diagnose and treat psychopathology. But what if the signal that we are trying to find depends on a balance of individual- and group-level analysis? Hyperalignment may provide part of a solution to this problem by preserving the characteristics of an individual's brain while also allowing for more accurate comparison at the group level. This suggests that the application of hyperalignment could improve the characterization of neural systems related to clinical disorders as well as the prediction and prevention of those disorders on the basis of neural data.

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