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Decontextualizing neuroscience: Opportunities and pitfalls of brain map correlations

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Understanding mechanisms of brain function and dysfunction is at the core of the neuroscience mission. However, our grasp of causal relationships between brain properties is hindered by a historical focus on single modalities neglecting the complex interplay between neural scales and features. Progress in neuroinformatics and the increasing availability of open datasets such as BigBrain have helped overcome this limitation by facilitating the contextualization of brain maps against cellular, metabolic, and network properties (**Fig1A**). Contextualization methods propose that quantifying spatial similarity between brain maps (or brain map correlations) may shed light on pathways of structure-function coupling, development, and disease.

Despite the rapid uptake of these methods, their potential pitfalls have received little attention (**Fig1B**). First, data contextualization studies often apply series of bivariate correlations to uncover potential relationships between brain maps. In addition to lack of justification for selected brain maps in these exploratory analyses, results are often described using causally ambiguous language that can overstate posited mechanistic relationships. Moreover, data contextualization studies tend to reuse reference datasets built from small and non-representative samples, particularly when these datasets are generated using costly and logistically complex methods. Yet, the generalizability of insights gained from these brain maps is unknown. Regarding data processing, problems with inter-modal and inter-subject alignment can introduce systematic regional bias in data contextualization studies. Together, these challenges can lead to correlational overreach, overfitting, circular reasoning, and limit findings to source data quality.

We propose a roadmap of practical guidelines operating at the level of study design, analysis pipelines, and interpretation of findings to develop best practices in data contextualization (**Fig1B**). First, researchers should anticipate whether data contextualization is best applied for confirmatory (i.e., hypothesis-driven) or exploratory purposes in their work. This choice should be clearly reported and justified to guide downstream interpretation of results. Second, we encourage frameworks considering different aspects of analytical uncertainty in the data contextualization pipeline, which could include quantitative estimates of co-registration and spatial normalization accuracy as well as regional and inter-individual data homogeneity. Third, correlative studies should ideally be complemented and/or confirmed by paradigms that approach causal inference at the level of study design (e.g., leveraging animal models for electrophysiological stimulation, optogenetic and chemogenetic modulation, or targeted lesions) and analytics (e.g., hierarchical models). Lastly, we advocate for increased data diversity through geographically and clinically broader data collection initiatives. Data augmentation could also leverage synthetic data generated from artificial intelligence techniques when additional data collection is not possible.

A multiscale understanding of neural systems requires analyzing and disentangling their components and interdependencies. While data contextualization has naturally lent itself to this endeavour, neglecting this technique's intrinsic limitations risks overstating its explanatory power on overarching principles of brain organization. We encourage open discussions in the neuroimaging community to refine data contextualization techniques and their implementation within paradigms better suited to mechanistic investigations of brain organization.

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