

Editorials

From associations and predictions to perturbations and mechanisms: Commentary on “Longer scans boost prediction and cut costs in brain-wide association studies”

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Brain-wide association studies (BWAS) are a research tool for discovering reproducible brain–phenotype associations but require massive sample sizes to achieve adequate power. Ooi and colleagues recently demonstrated that longer fMRI scans in fewer participants can outperform short scans in large samples. While acknowledging the practical value of this approach, we highlight three critical considerations: population representativeness, cohort-specific feasibility constraints, and the distinction between predictive optimization and mechanistic understanding. We also outline complementary strategies that can enhance predictive power without solely relying on increased scan duration.

Brain-wide association studies (BWAS) are a research tool for discovering reproducible brain–phenotype associations, providing constraints and hypotheses for downstream mechanistic and causal investigations.¹ Ooi and colleagues² address a long-standing design problem in BWAS: How to trade off scan duration, sample size, and cost. This approach reframes BWAS design as a joint optimization problem rather than a simple power calculation over sample size (when scan time has already been determined). Their central result is that phenotype prediction accuracy scales with both sample size and total scan duration, and that longer scans in fewer persons can often be more cost-effective than recruiting additional participants for shorter scans. This result will no doubt exert a substantial influence across the ecosystem of large-scale neuroimaging studies, from funding through design to analysis.

The authors first decompose variance terms into those scaling with $1/N$ and $1/(NT)$, where N is the sample size and T is the scan duration. This provides an intuitively appealing account of two distinct regimes. At short scan durations, the $1/(NT)$ term dominates, rendering scan time and sample size partially interchangeable. As scan time T increases and functional connectivity estimates saturate, the $1/N$ term begins to dominate performance, such that additional gains are driven primarily by larger samples rather than longer scans. Importantly, when participant overhead costs are considered, this framework also explains why very

short scans (for example, 10 minutes) are rarely cost-efficient: they operate in a regime where modest increases in scan time yield disproportionate improvements in prediction at modest extra cost. Under generic assumptions, they suggest that 30 min scans are the most cost-effective, yielding 22% cost savings over 10 min scans. The accompanying tool strengthens the paper’s practical impact by making these trade-offs explicit for study design.

However, the logic of economic optimization raises broader questions about what is gained and what may be lost when BWAS are designed primarily around predictive efficiency. One such issue concerns population representation. It is already appreciated that existing population imaging data sets do not properly represent the broader communities on which they are drawn, with Indigenous and First Nations people particularly poorly represented or misrepresented³: This issue limits the generalizability of BWAS studies, particularly their relevance for applications such as patient stratification, clinical trial screening or biomarker validation in diverse clinical populations. Choosing longer scans in smaller samples risks exacerbating the well-documented under-representation of minority populations in neuroimaging, including Indigenous peoples, ethnic minorities, and socially marginalized groups.⁴ A highly reliable model trained on a small, homogeneous cohort may achieve impressive prediction metrics while systematically failing to generalize across populations.

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While a single study might sacrifice predictive power in pursuit of maximal diversity, an alternative framing is that the field may benefit from multiple, population-specific BWAS studies. Each study would then be optimized for a defined demographic or clinical subpopulation. If distinct populations exhibit different brain–phenotype mappings, then a powerful predictor across specific subgroups may ultimately be more clinically useful than a diluted predictor for all. However, implementing such a stratified research program raises its own challenges, such as defining meaningful subgroup boundaries, and avoiding excessive partitioning that could hinder integration and generalization of findings across studies. The optimal path likely involves both: population-specific optimization where distinct mappings exist, and deliberate efforts to include underrepresented groups like those varying in socioeconomic status, educational attainment, and rural versus urban living conditions.

Age represents another dimension along which longer scan duration affects feasibility. Ooi et al.'s 30-minute recommendation derives primarily from young cohorts. Older adults face distinct challenges; for example, prolonged stillness in an uncomfortable position can lead to pain.⁵ Even if this does not lead to premature scan termination, this issue will introduce an interaction between age and data quality. Head motion artifacts accumulate over time, introducing systematic biases in connectivity estimates that particularly affect long-range connections and subcortical regions.^{6,7} Age-specific scan time optimization may be warranted, particularly for older or specific clinical populations such as people with attention deficit disorder.⁸

The practical constraints we highlight here, such as age, participant comfort, and motion, are illustrative examples from a much larger space of feasibility considerations. These include scanner harmonization across sites, image quality assurance, task selection and optimization, participant retention, socioeconomic status, educational attainment, rural versus urban living conditions and site-specific logistical and ethical requirements. Effective study design requires jointly evaluating all relevant constraints alongside the acquisition parameters optimized by Ooi et al., ideally within their accompanying cost-optimization framework.

To their credit, the authors explicitly acknowledge the tension between cost-efficiency and representativeness, noting that non-economic considerations such as representativeness and generalizability may require prioritizing larger samples even at the expense of scan time. They also raise an important counterpoint: for harder-to-recruit subpopulations, it may be more efficient to scan fewer par-

ticipants longer than to exclude them entirely. This observation underscores an important point of the paper: Representation can be treated as a design constraint in the accompanying tool.

Beyond issues of equity and generalizability lies a more fundamental limitation of BWAS which are optimized for association, not for elucidating mechanistic principles of brain organization. While Ooi et al. do not claim to address mechanistic questions, it is worth considering how their recommendations interact with broader scientific goals. Even multivariate and predictive (out of sample) BWAS findings remain fundamentally correlational. They identify patterns that covary with phenotypes, but they do not specify causal structure, directionality, or generative processes. BWAS also lack counterfactual structure. That is, mechanistic understanding requires knowing what would change if a component were perturbed through lesions, stimulation, or neuropharmacology. Cross-sectional associations or out-of-sample prediction, no matter how robust or well-powered, cannot distinguish drivers from downstream effects or compensatory responses.

Although the field has endeavoured to highlight the importance of smaller studies⁹ which could seek to interrogate causal or mechanistic processes, such reminders are often overlooked in headline reports which could in turn misguide strategy and funding decisions. This limitation is compounded by the use of static representations in BWAS, such as time-averaged functional connectivity. Candidate mechanisms of large-scale brain organization such as metastability,¹⁰ controllability,¹¹ and wave propagation¹² are inherently dynamical. Distinct underlying mechanisms can give rise to similar static summaries,¹³ creating a many-to-one mapping from mechanisms to measurement. Longer scans may assist resolution of this identifiability problem, but only when the data are subject to suitable, dynamic analytic approaches.¹⁴ Specific methods that show promise include time-varying functional connectivity analyses,¹⁵ hidden Markov models that identify recurrent brain states,^{16,17} and dynamic-systems approaches that characterize the temporal structure of neural dynamics.^{10, 14,18} Multivariate and cross-modal methods further complement these approaches by capturing the multidimensional structure of brain–phenotype relationships that univariate or static summaries may miss (see [Box 1](#) for a summary of these and other complementary strategies). Longer scan durations, as advocated by Ooi et al., naturally benefit these dynamic approaches by providing the sample length needed to accumulate the temporal fingerprints of transient brain states and their phenotypic correlates.

Box 1. How to boost BWAS power beyond sample size and scan duration

1. Align brain states

Task-fMRI or other state manipulations like naturalistic stimuli often outperform resting-state for trait prediction by reducing irrelevant variance and increasing functional specificity.^{19–21}

2. Employ subject-specific mapping

Subject-specific parcellations and precision mapping reduce misalignment noise introduced by group atlases, potentially increasing signal-to-noise without longer scans.^{22,23}

3. Optimize acquisition protocols

Reduce acquisition noise by employing customized sequences such as multi-echo fMRI²⁴ (note however that Ooi et al. suggest a lesser role for this; their Extended Data Figure 8f).

4. Constrain the feature space

Restricting analyses to smaller feature spaces or to behavioural data acquired during scanning.^{25,26}

5. Improve phenotypic measurement

Improving the reliability and psychometric properties of the behavioral data²⁷ (note however that Ooi et al. suggest a lesser role for this; their Extended Data Figure 8c).

6. Within-subject and longitudinal designs

Using participants as their own controls removes large inter-individual nuisance variance and increases sensitivity to meaningful changes.²⁸

7. Generative and dynamical constraints

Model-based approaches (e.g., network control, dynamical systems) reduce hypothesis space and improve identifiability, yielding power through theory rather than scale.²⁹

8. Multivariate and cross-modal approaches

Multivariate methods (e.g., canonical correlation analysis, partial least squares) can capture the joint, multidimensional structure of brain–phenotype relationships, potentially mitigating the power limitations inherent in mass-univariate BWAS designs by leveraging shared variance across multiple brain and behavioural measures simultaneously.³⁰ However, multivariate methods are vulnerable to the same risks of effect to dilution if exposed to the same types of scanner and phenotype heterogeneity as univariate methods.³¹

Whereas Ooi et al. focus on the total scan volume (through N and T), substantial work has identified other factors that can also improve individual prediction accuracy. Notably, they show that employing task-fMRI may reduce the optimal scan time from 30 to 20 minutes (Fig. 5b)²: Similar reductions may also pertain to using naturalistic stimuli such as movies.³² In [Box 1](#) we summarize existing and emerging strategies spanning acquisition, design, preprocessing and modeling choices. Such approaches can be implemented using existing toolboxes, hence at substantially lower cost than longer scans and/or additional recruitments. Effective BWAS design therefore requires jointly optimizing across these dimensions, recognizing that gains in one area may offset requirements in others.

These observations do not diminish the importance of the work of Ooi et al. Rather, they are proposed to clarify the appropriate role of BWAS within a broader scientific programme. BWAS excel at mapping the statistical fingerprint of brain–behavior relationships across populations. BWAS studies can (and have) falsified overly local theories, highlight optimal analysis strategies and provide benchmarks against which generative models can be tested.

In summary, Ooi et al. make an important contribution to the methodological foundations of BWAS and provide actionable guidance for study design. Simultaneously, the authors implicitly remind the field that optimization for out-of-sample prediction is not synonymous with explanation. More broadly, the BWAS framework including the rigorous cost-benefit analysis undertaken by Ooi et al. serves

as a powerful lens through which the field can appreciate the many variables that must be addressed before fMRI-based biomarkers can achieve clinical relevance. The challenge moving forward is therefore to integrate the statistical power of BWAS with designs and models that address dynamics, causality, and population diversity, so that efficiency gains serve not only prediction, but understanding.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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