Precision Imaging Drug Trials: Quantifying the Impact of Study Design on fMRI Biomarker Sensitivity and Statistical Power

Submitter Joshua Siegel

Affiliation New York University Grossman School of Medicine

SUBMISSION DETAILS

I agree to provide poster pdf for attendee download. Yes

I have used the poster abstract template to develop my abstract. Yes

Methodological Issue Being Addressed Reliable biomarkers for brain circuit target engagement are critical for advancing drug development in central nervous system (CNS) disorders. fMRI has good brain coverage and spatial resolution, but has demonstrated high variability (in brain anatomy and drug effects), low signal-to-noise ratio (SNR), and lack of validated targets, preventing its adoption in clinical development.

Introduction Precision functional mapping (PFM) is an approach which uses a single individual's resting fMRI to precisely define functional areas and networks [common across humans]. The fundamental paradigm shift behind PFM is the realization that individual differences dilutes neuroimaging results and individual-defined functional circuits and within-subject analyses dramatically enhances power. We previously introduced the Precision Imaging Drug Trial (PIDT) methodology, integrating Precision Functional Mapping (PFM), within-subject repeated measures, and advanced MRI acquisition and processing, enhancing sensitivity for detecting drug effects. Here, we empirically evaluate how specific study design choices influence effect size, statistical power, and sample size requirements using methylphenidate-induced reductions in somatomotor network functional connectivity (FC) as a test case.

Methods We assessed sensitivity to a known drug FC biomarker (stimulant drugs decreased FC in motor cortex) in a cross-sectional dataset from the Adolescent Brain Cognitive Development (ABCD) cohort (N=4,320, stimulant users N=390) and a longitudinal precision fMRI dataset with controlled methylphenidate administration (N = 7). We used Bayesian predictive probabilities and bootstrapping validation to extrapolate expected power to detect a drug effect across a variety of study designs (cross-section vs cross-over, multiple vs single visits per condition, individualized versus group parcellation).

Results A parallel arm design revealed the worst power (N = 270 participants to achieve 90% power). A controlled within-participant design was far more sensitive (N = 43 participants to achieve 90% power). Adding repeated, longer duration fMRI scans over multiple days further boosted power (N = 22 participants to achieve 90% power), and adding individual-specific parcellation achieved the best power N = 17 participants to achieve 90% power). A cost optimization model finds that a within-participant design with two visits per condition is ideal.

Conclusion Study design, individualized parcellation, and measurement frequency critically

impacted statistical efficiency. Within-participant repeated visit designs integrating advanced MRI acquisition and Precision Functional Mapping (PFM) can dramatically increase sensitivity of fMRI, reducing sample size needed and improving cost-effectiveness for drug biomarker research.

Co-Authors

Joshua Siegel[1], Benjamin Kay[2], Russell ("Taki") Shinohara[3], Subha Subramanian[4], Nico Dosenbach[2]

[1] New York University Grossman School of Medicine

[2] Washington University in Saint Louis

[3] Perelman School of Medicine, University of Pennsylvania

[4] Beth Israel Deaconess Medical Center and Harvard Medical School

Keywords

Keywords
imaging biomarkers
drug development
psychopharmacology
fMRI

Guidelines I have read and understand the Poster Guidelines

Disclosures JSS and NUD are co-authors of a provisional patent (Patent 020949/US 15060-1787) for the use of precision functional mapping for measuring target engagement by experimental therapeutics. Within the last year, JSS received consulting fees from Otsuka and Janssen R&D. These potential conflicts of interest have been reviewed and are managed by New York University Langone Health.