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

Joshua S Siegel[1], Benjamin Kay[2], Taki Shinohara[3], Timothy O Laumann[2], Evan M Gordon[2], Nicholas V Metcalf[2], Nico UF Dosenbach[2]

1: New York University, Grossman School of Medicine, New York, NY, USA. 2: Washington University School of Medicine, St Louis, MO, USA. 3: University of Pennsylvania, PA, USA.

Methodological Issue Being Addressed

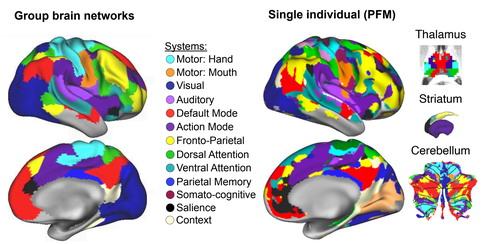
Methodological issue: Reliable biomarkers for brain circuit target engagement are critical for advancing drug development in central nervous system (CNS) disorders. fMRI has good brain coverage and spatial resolution, but has demonstrated high variability (in brain anatomy and drug effects), low signal-to-noise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

Aim: empirically evaluate how individualized network mapping (avoiding group averaging) and specific fMRI biomarker study design choices influence effect size, statistical power, and sample size req. using a well-established FC biomarker as a test case.

Methodological Advance: Precision Functional Mapping

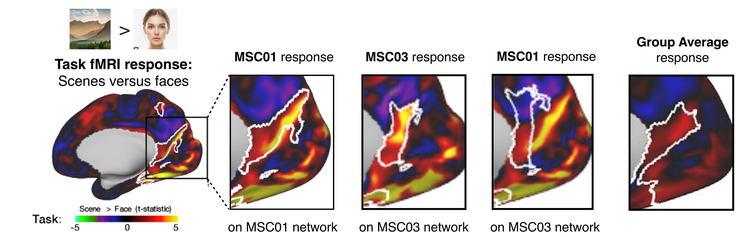
The paradigm shift: individual-defined functional circuits and within-subject (N=1) analysis overcomes problems caused by averaging to common structural atlas.

Precision functional mapping (PFM): Define functional areas and networks from resting state functional connectivity (RSFC) data in single individuals (using infomap or other algorithms), use individual's areas + within-subject study design to interpret activation/connectivity data.

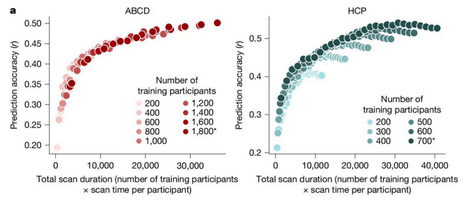


Individual brains [functional networks] do not look like the average brain

- When brain activity does not align across individuals, averaging decreases effect sizes



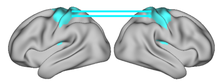
Task fMRI contrast 'Scene > Face' maps (t-statistics) for two individuals (MSC01, MSC03) and for the group. Boundaries of each individual's 'context association network', defined from independently acquired resting fMRI, are overlaid in white on task contrast (left two rectangles), and then mismatched across individuals (third rectangle) and Group average (fourth rectangle)

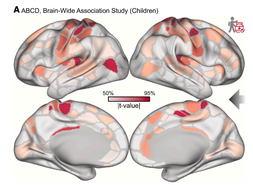


"Longer scans boost prediction and cut costs in brain-wide association studies" Ooi et al., 2025, Nature

METHODS: A multi-dataset evaluation of biomarker effect size

We assessed sensitivity to a known drug FC biomarker (stimulant drugs decreased somatomotor FC) across three methylphenidate resting fMRI datasets with very different study design and parameters: 1) a cross-sectional dataset from the Adolescent Brain Cognitive Development (ABCD) cohort (N=11,875; stimulant users N=390) 2) a longitudinal precision fMRI dataset with controlled methylphenidate administration (N = 7), and 3) a cross-over study of PV/PO methylphenidate with 90 min of PET/MRI acquisition at four visits.



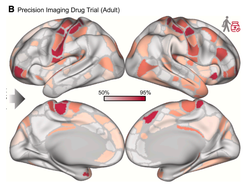


Dataset 1 — Cross-sectional (Kay et al., *Cell*, 2025)

- Study type: Cross-sectional analysis from the ABCD cohort
- Sample:
  - Total cohort: N = 11,875 (ages 8–11)
  - Passed rigorous imaging/data QC: N = 4,320
  - Reported stimulant use on day of scan: N = 390
- Sites/scanners:
  - Data collected across 21 sites
  - Harmonized 3T GE, Philips, and Siemens platforms
- MRI protocol:
  - Structural + task fMRI
  - Resting-state fMRI: up to 4 × 5-min runs (TR = 800 ms; up to 20 min total)
- Model covariates/controls: ADHD status, Sex/gender, Other medication use

Dataset 2 — Longitudinal precision fMRI trial (Siegel et al., *Nature*, 2024)

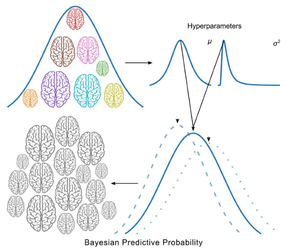
- Study type: Within-subject longitudinal drug challenge with precision fMRI mapping
- Sample: Healthy young adults (N = 7; ages 19–45)
- Interventions:
  - Psilocybin: 25 mg
  - Methylphenidate: 40 mg
- Design/timing:
  - Drug sessions separated by 1–2 weeks
  - Repeated MRI sessions before, during, between, and after both drug conditions (average of 18 visits/participant)
- Primary analytic approach:
  - Within-subject precision functional mapping to quantify individual-specific FC changes

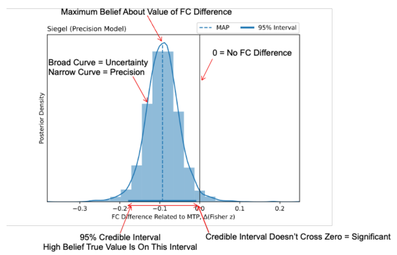


Dataset 3 — Classic cross-over biomarker study (Tomasi et al., *PNAS*, 2023)

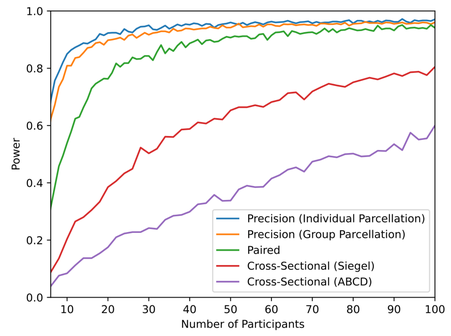
- Study type: Cross-over biomarker design (3 conditions, separate days)
- Sample: Healthy adults (N = 20; mean age 36.1; 9 females)
- Session structure: 3 scanning days per participant
- Pharmacologic conditions:
  - Oral MP 60 mg + IV placebo (0.3 cc saline)
  - Oral placebo + IV MP 0.25 mg/kg (in 3 cc sterile water)
  - Double placebo
- Imaging platform/protocol:
  - Simultaneous PET/MRI on 3T Biograph mMR with 12-channel head coil
  - PET + resting-state fMRI acquired concurrently over 90 minutes

We used this empirical data + **Bayesian predictive probabilities** 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: Assessing biomarker variance and effects size



Sample sizes needed to detect a stimulant biomarker…

	Data Cleaning	Cross-over design	Same Scanning	Individual-defined areas	N to achieve 90% Power:
Parallel arm, 1 visit	+	-	-	-	270
Cross-over, conventional	+	+	-	-	43
Cross-over, multi-visit	+	+	+	-	20
Cross-over, multi-visit, PFM	+	+	+	+	17

A parallel arm design revealed the worst power (**N = 270** participants needed to achieve 90% power). A controlled within-participant design was far more sensitive (**N = 43** participants needed to achieve 90% power). Adding repeated, longer duration fMRI scans over multiple days further boosted power (**N = 22** for 90% power), and adding individual-specific parcellation achieved the best power (**N = 17** for 90% power).

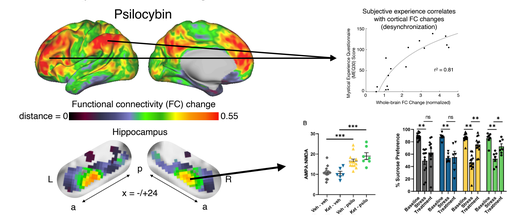
Next Step: Build a cost optimization model finds that a within-participant design with two visits per condition is ideal. Include Dataset 3.

CONCLUSIONS

Study design, individual parcellation, and measurement frequency critically impacted efficiency. Cross-over repeated visit designs with advanced MRI and Precision Functional Mapping (PFM) dramatically increase sensitivity of fMRI and improve cost-effectiveness for drug biomarker research.

Future Directions: A Biomarker Platform

Precision Imaging Trial to rapidly and cost-effectively assess target engagement… for a non-hallucinogenic 5HT2A agonist



Cortical desynchronization is a biomarker of psychedelic effects

Hippocampal FC change is a biomarker of antidepressant-like effects

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CONTACT: joshua.siegel@nyulangone.org

NYU Langone Health

Center for Psychedelic Medicine