

Precision Functional Mapping Trials - A biomarker platform for neuropsychiatric drug development

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Methodological Issue Being Addressed

In psychiatry, rodent disease models are poor, pivotal trials are expensive, success rates are lower than other fields. Reliable biomarkers for brain circuit target engagement are critical for advancing drug development in CNS disorders.

"In our view, resolution of technical uncertainty early in development, especially whether or not a molecule engages its target and has desired pharmacological activity in humans is necessary to improve R&D productivity." Paul et al., 2010

EEG - low cost but poor resolution, cannot resolve deep structures

PET - works well if you have the right radio tracer and are confident that occupancy = agonism

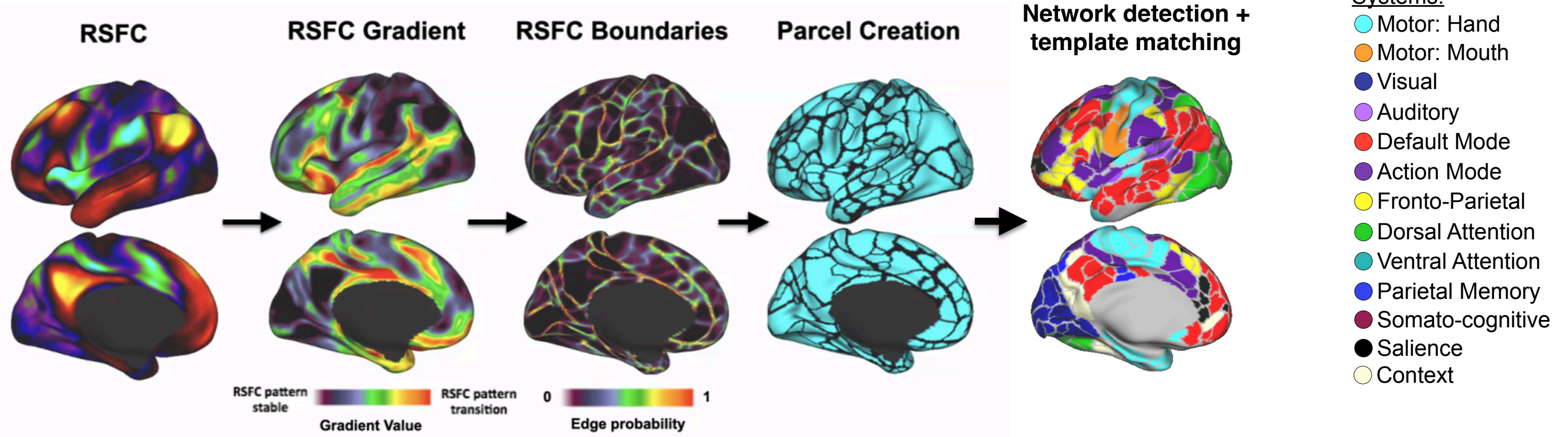
fMRI: good spatial resolution, big databases. BUT group averaging, high variability, and low SNR, have limited utility for drug development.

Introduction & General (Precision Imaging) Methods

The paradigm shift: individual-defined functional circuits and within-subject (N=1) analysis. No more averaging to common structural atlas.

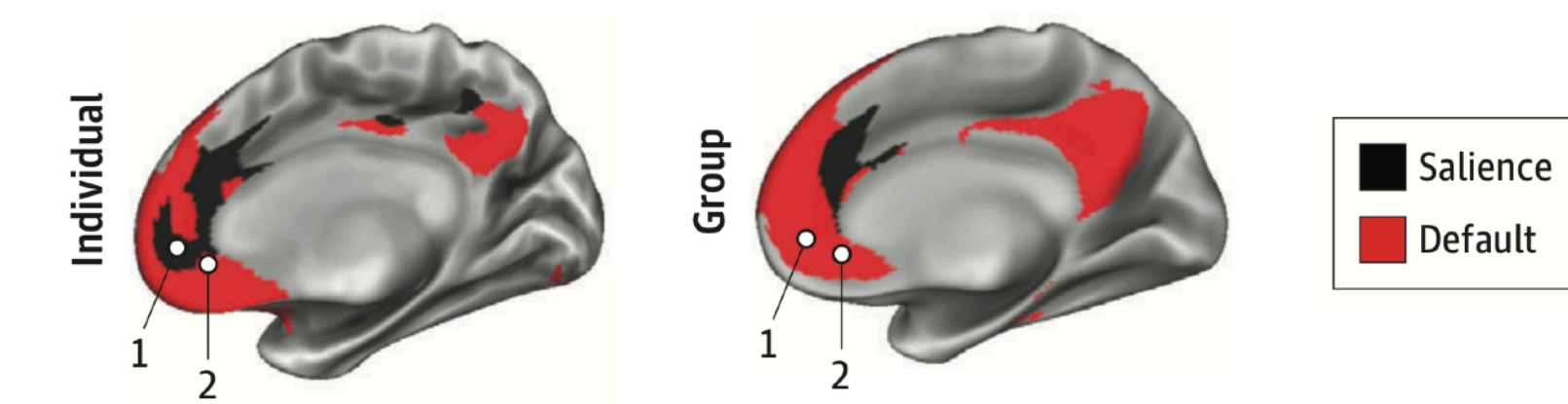
Precision functional mapping (PFM): Define functional areas and networks from resting state functional connectivity (RSFC) data in single individuals (using infomap or other algorithms), use individual's areas + within-subject study design to interpret activation/connectivity data.

From RSFC maps to brain area/network detection in group or single individual data

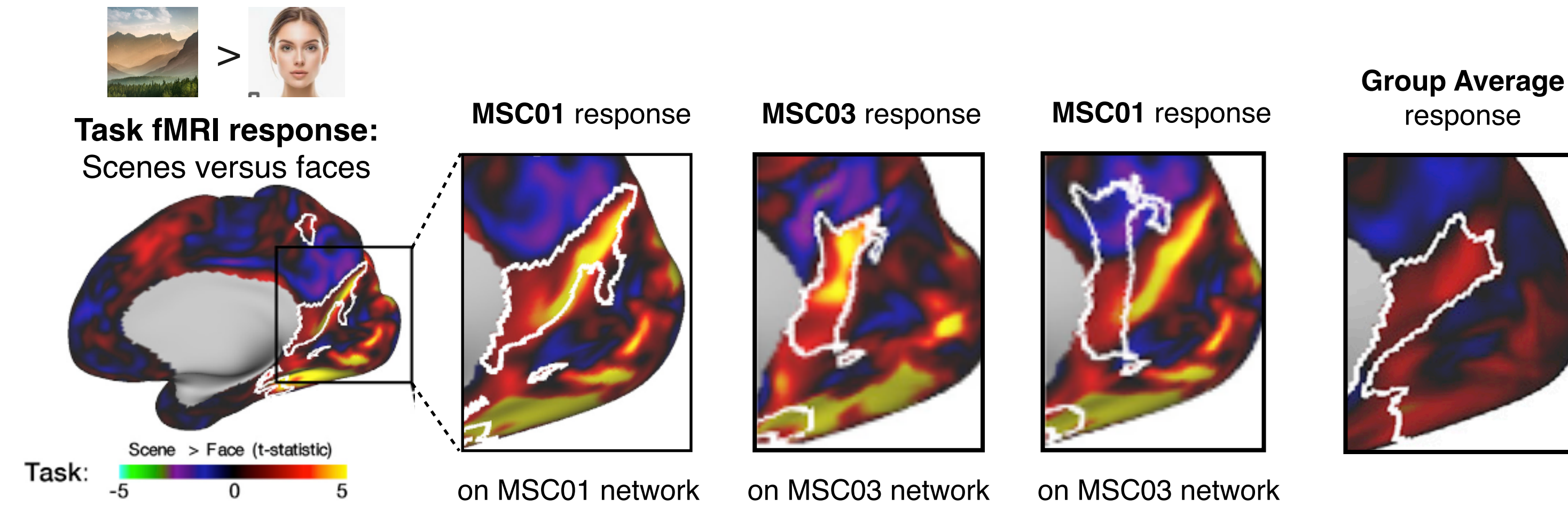


- Transitions in RSFC represent boundaries between functional areas. network detection identifies canonical brain areas/networks

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



- Individual brain activity does not align. Thus, 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)

CONCLUSIONS



Precision Functional Mapping is a novel approach to fMRI with powerful potential for early-phase neuropsychiatric drug development.



PFM can provide sensitive biomarkers for psychedelics, non-hallucinogenic analogs, stimulants, antipsychotics, and other targets.

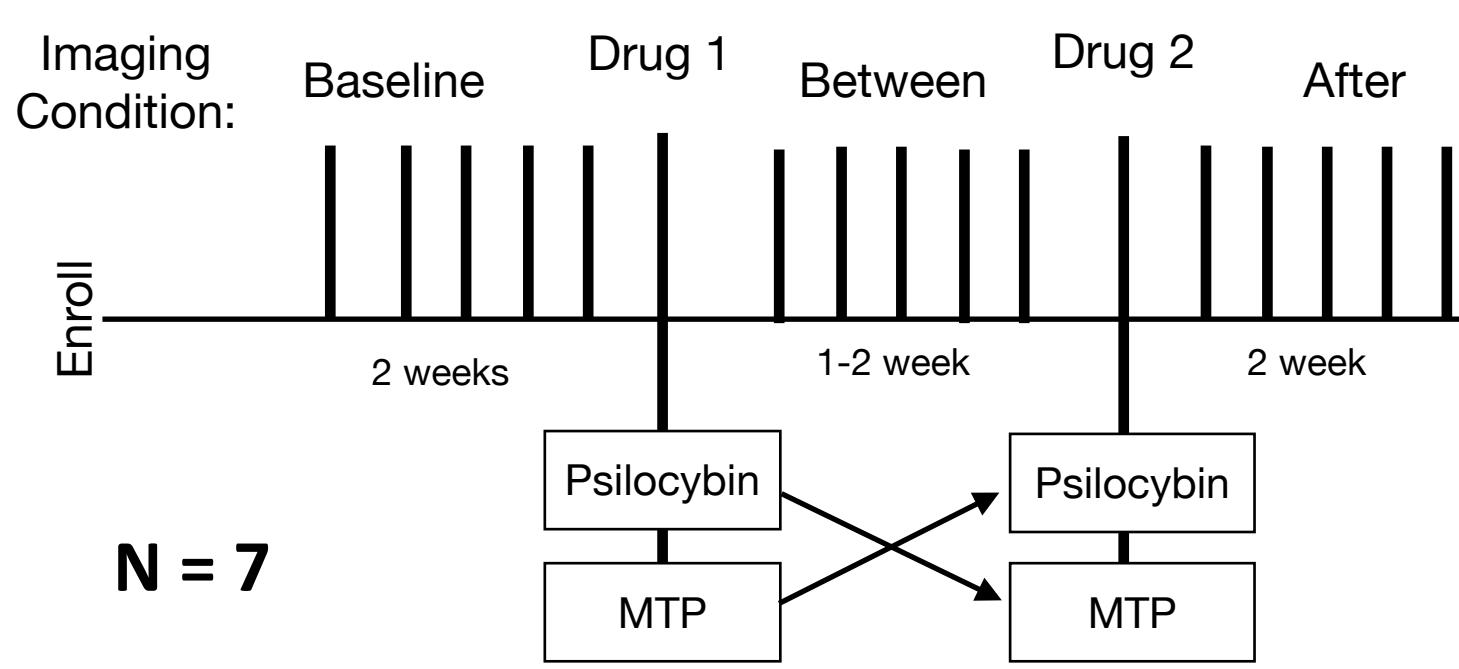
METHODS: Psilocybin & Stimulant (Siegel et al., Nature 2024)

Participants:
Key inclusion criteria:
• Age 18-45 years
• Medically healthy
• Prior psychedelic exposure

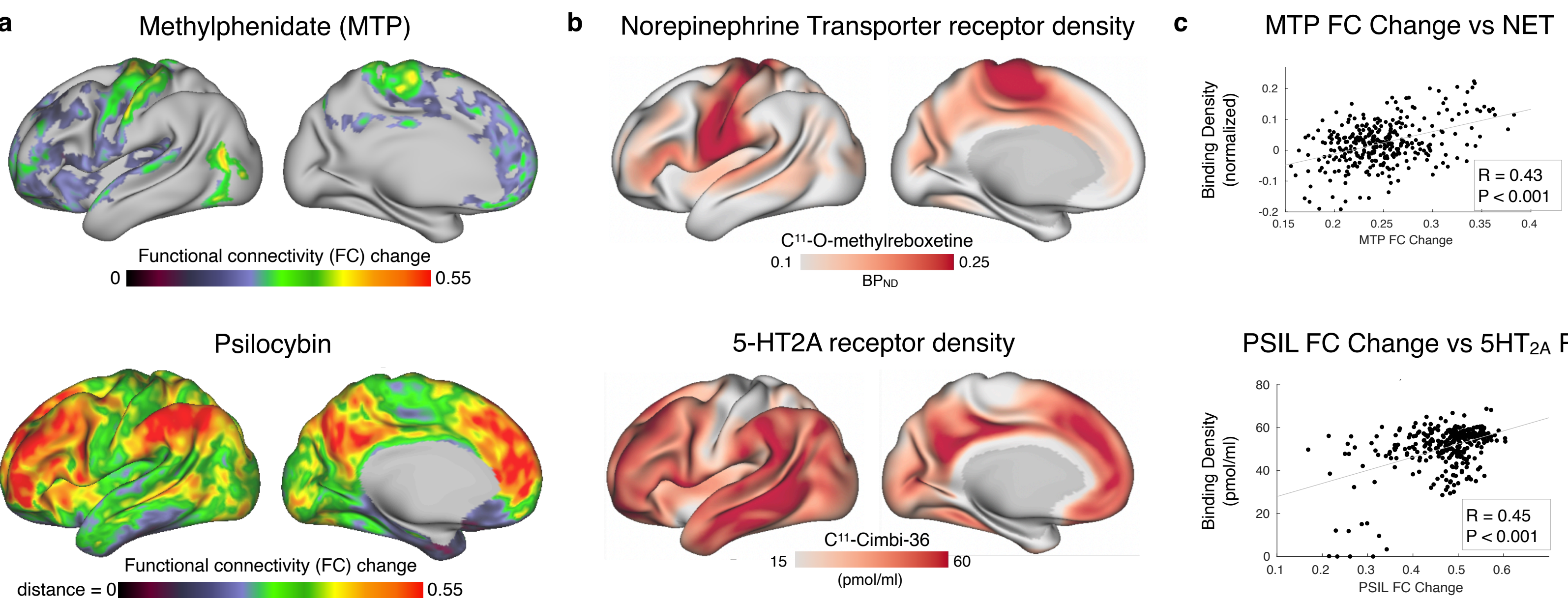
Key exclusion criteria:
• Psychiatric diagnosis
• Psychiatric medications

Intervention:
Psilocybin 25 mg

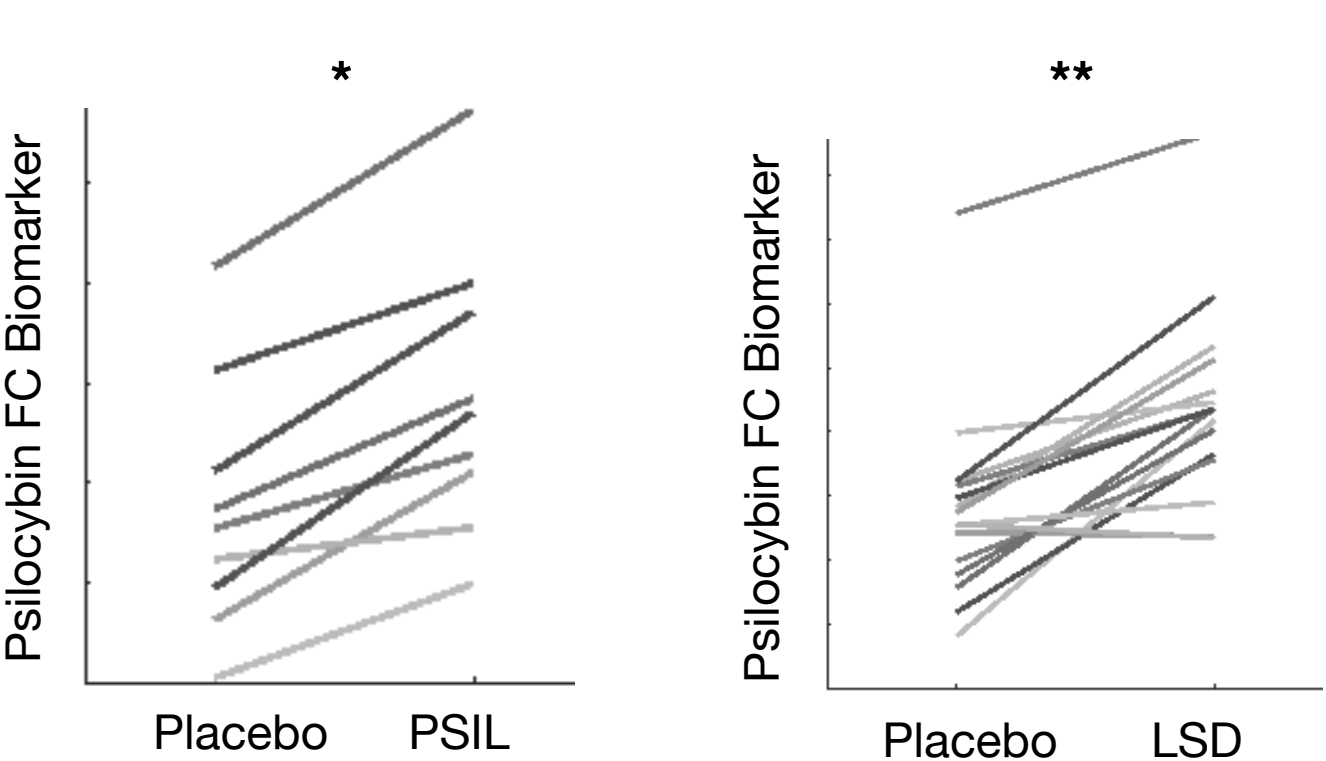
Control:
Methylphenidate 40 mg



RESULTS



- FC-based biomarkers for Psilocybin and MTP align well with PET-based 5HT-2A and NE Transporter maps



- FC-based biomarker for Psilocybin (loss of FC within the default mode network, loss of segregation between networks) generalizes across datasets and across psychedelics.

METHODS: Assessing biomarker variance and effects size

We compared an *a priori* biomarker (stimulant -> ↓ motor network FC) across different datasets and methods.

Model 1: Adolescent Brain Cognitive Development Cohort. N=4,320 (390). many different stimulants, mixed effects model using cross-sectional design and controlling for covariates

Model 2: ABCD data, but using strict exclusion of high head motion subjects (N=4,035)

Model 3: PIDT Data, Unpaired, group parcels. LME does not include 'subject', unpaired t-test.

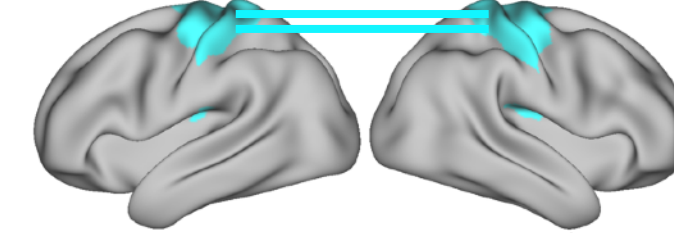
LME Wilkinsonian Notation: GL_RSN_FC ~ class + FD + task + task*class

Model 4: Paired, group parcels: LME includes 'subject', analogous to a paired t-test.

LME Wilkinsonian Notation: GL_RSN_FC ~ class + FD + task + task*class + (1 | SubID)

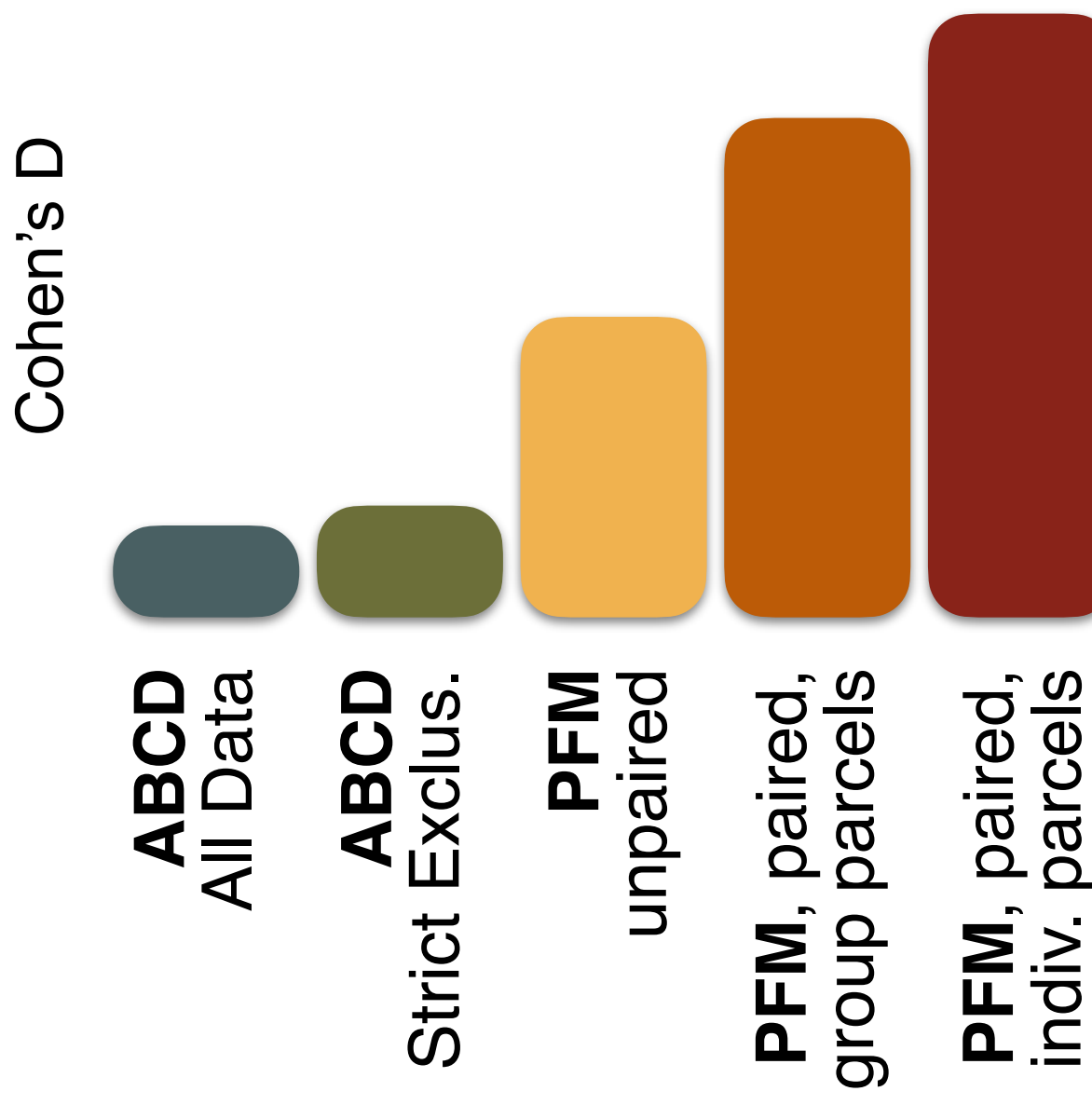
Model 5: Paired, individual-defined parcels (using Laumann edge detection package + Gordon infomap)

LME Wilkinsonian Notation: Ind_RSN_FC ~ class + FD + task + task*class + (1 | SubID)

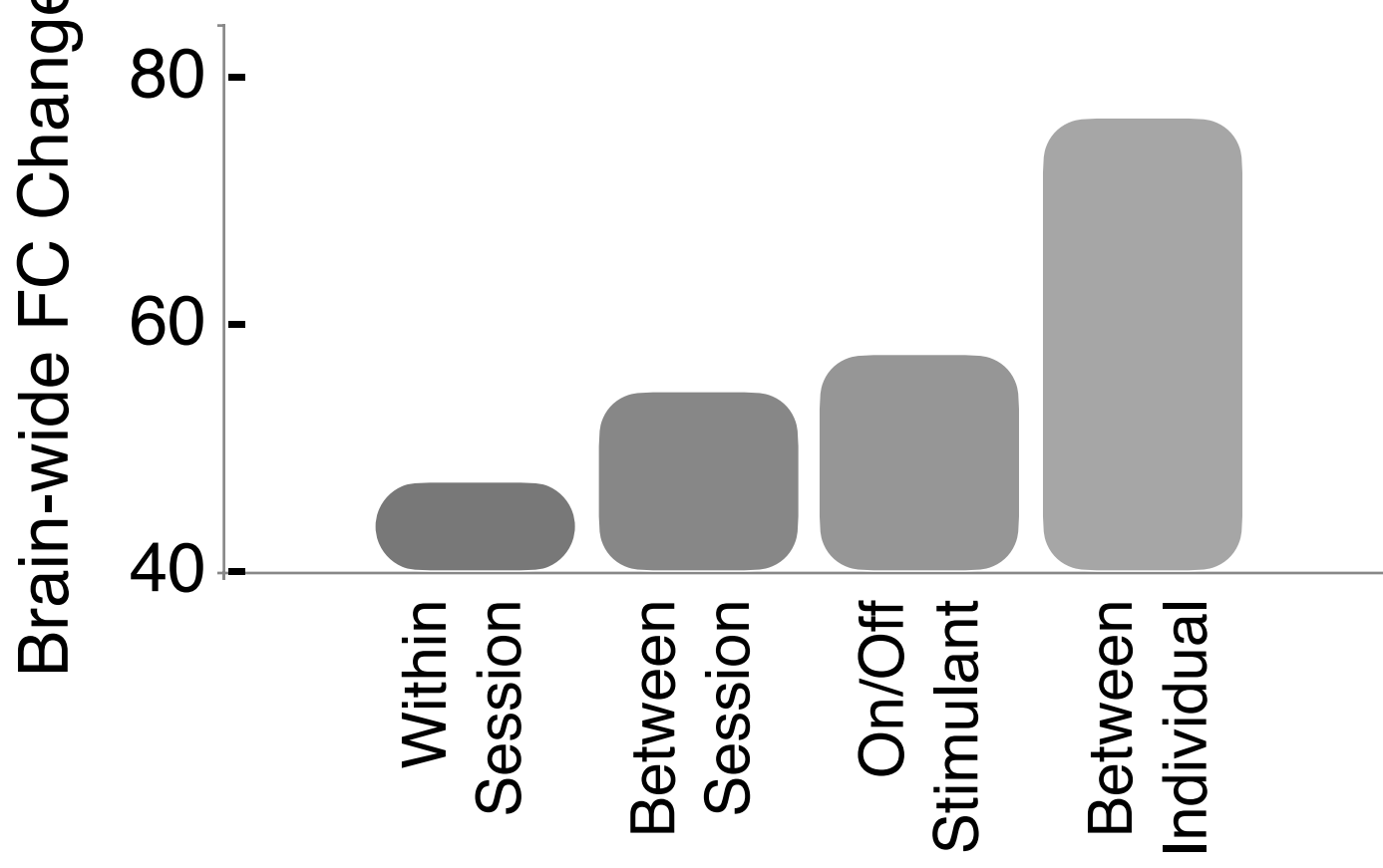


RESULTS

Effect size of Stimulant on FC Biomarker



Sources of Measurement Variability in PFM Dataset



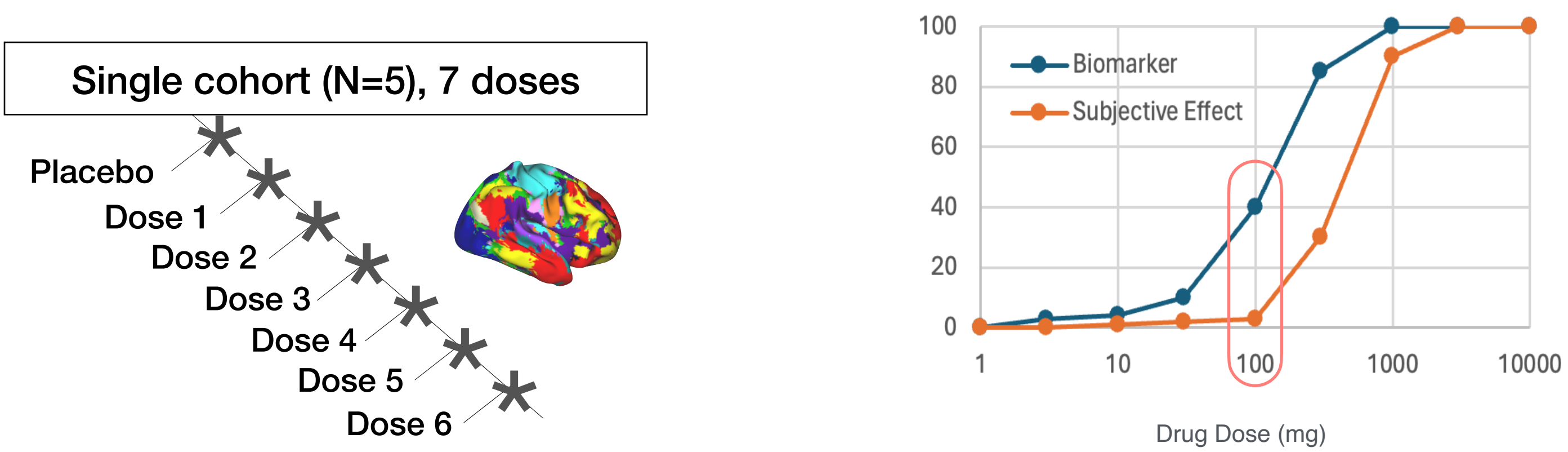
N to achieve 95% Power: 336 226 34 5 4

- Precision Functional Mapping design (cross-over, dense sampling) yields biomarker effect size much larger than conventional fMRI. Sample size needed to detect an effect drops from 100s to 4!

Future Directions: A Biomarker Platform

PFM + repeat imaging on/off drug: rapidly and cost-effectively assess target engagement.

Phase 1b "Precision Functional Mapping Trial" Study Design for Novel 5HT2A agonist



REFERENCES:

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Gordon, E. M. et al. (2017) Precision Functional Mapping of Individual Human Brains. *Neuron* 95, 791-807.e7.
Siegel, J. S. et al., (2024). Psilocybin desynchronizes the human brain. *Nature*, 632(8023), 131-138.
Siegel, J. S. (2024). Precision functional mapping for target engagement in drug development. *Neuropsychopharmacology*, 339-340.

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