Reference Ranges of Healthy Brain Network Activity to Inform CNS Treatment Development

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What is the Methodological Issue Being Addressed? We previously introduced a quantitative capability of multi-echo functional magnetic resonance imaging (ME-fMRI) that improves the sensitivity, specificity, and reliability of brain activity measurements, positioning fMRI as a powerful tool to identify objective disease-specific markers. The present work demonstrates that quantitative ME-fMRI can identify task and disease state perturbations in brain activity at the subject level and highlights its utility for the monitoring of treatment effects in CNS trials.

Introduction ME-fMRI holds promise as an engine for biomarker discovery in its ability to significantly attenuate artifacts, improve BOLD signal sensitivity, and yield high resolution images of brain activity in individual subjects. However, the interpretation of single-subject estimates is limited without a relevant reference for comparison.

Our group reported on a ME-fMRI quantitative unit that standardizes BOLD signal and expresses changes in brain activity in units of magnitude. Preliminary evidence with this autocalibrated relaxometry unit (ARU), which links neural signal to perfusion dynamics, demonstrated that brain activity measured with ARU, compared to percent signal change, boosts contrast-to noise, differentiates across functional brain networks, and improves test-retest reliability. We hypothesize that brain activity expressed in ARU can therefore be meaningfully compared across individuals and conditions, and here examined whether ranges of healthy functional brain network expression can be derived akin to laboratory blood tests. We reasoned that as an intrinsically calibrated measure of BOLD signal, ARU measured during task and/or disease would fall outside the ranges in predictable ways. These results would provide evidence for the utility of healthy functional brain network ranges in disease-specific biomarker discovery.

Methods We first tested the stability of ranges calculated at rest in a set of canonical large-scale brain networks from healthy individuals across the adult lifespan. Over 500 previously published resting-state ME-fMRI datasets were aggregated. Participant time series were statistically fit against a set of template-based network maps. For each network, a summary score was calculated to quantify the network's magnitude in ARU. Cross-validation testing was performed to assess the stability of each network distribution and establish ranges.

We then examined whether the ranges were sensitive to state differences in neuropsychology and pathology. Two publicly available ME-fMRI datasets examined healthy task-evoked (motor, n=25, and language, n=40) brain activity relative to resting-state ranges. Resting ME-fMRI datasets from

two non-healthy nicotine-dependent patients, shared through collaborations, tested the sensitivity of ranges to disease. Z scores captured deviation from ranges.

Results Ranges for all networks are reported. ARU during task states was largely elevated in networks corresponding to the associated cognitive function, but Z values varied across participants (-.6-7.8). Individuals with nicotine addiction had lower subcortical and elevated attention ARU values relative to the healthy population.

Conclusion As part of ongoing efforts toward novel quantitative ME-fMRI methods, we present initial evidence that stable reference ranges of healthy brain network activity can be derived with sensitivity to state changes. Future work will focus on improving effect sizes and condition-dependent identifiability of patients. The ability to detect brain-wide patterns of deviation with simplified network scores holds significant promise in biomarker development for CNS treatment indication and monitoring.

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Keywords

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