# Quantitative, Standardized Brain Network Activity Measures to Inform CNS Treatment Development

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## Methodological Issue Addressed

- CNS trials are hampered by a lack of reliable neurobiological information to accelerate and de-risk therapeutic development.
- The present study tested whether a novel quantitative functional MRI (fMRI) technique could meet necessary conditions to derive standard measurements of neuronal activity for a set of canonical brain networks.

## Background

- Blood oxygenation level dependent (BOLD) fMRI is widely used to study functional neuroanatomy along with mechanisms of disease and drug action.
- High susceptibility to artifact yields inconsistent data quality, precluding widespread uptake in clinical trials.
- Multi-echo (ME) fMRI sequences acquire more data (at little-to-no cost), allowing sophisticated modeling of neural and non-neural signal[12].

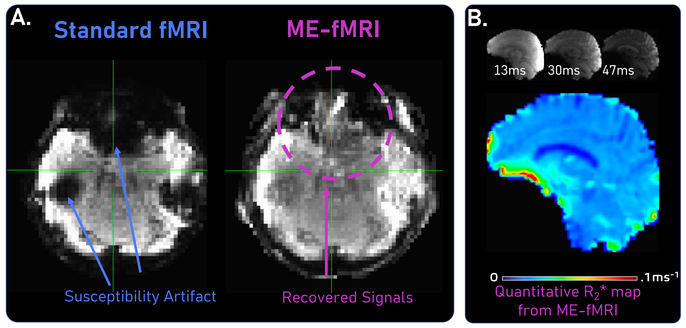



**Figure 1 | A.** ME-fMRI (right) demonstrates reduced noise and improved sensitivity to signal in regions susceptible to signal dropout compared to standard single-echo fMRI (left). **B.** By collecting additional images, ME-fMRI acquisitions use relaxometry to calculate R2* maps to serve as the basis for quantitative metrics of neural activity.

- In this way, ME-fMRI can take advantage of NMR relaxometry ($R_2$*) to derive neural signal in quantitatively meaningful units linked to oxyhemoglobin concentration.

**ME-fMRI Relaxometry Equation**

$$\Delta S/S = -TE \cdot \Delta R_2^*$$

**Iron Susceptibility Equation**

$$R_2^* = R_2 + \varphi_{Fe^\star}[Fe^\star]$$

*Measured(fit in voxel* *of gray matter* *Relaxivity of Iron: factor out* *Concentration in voxel*

**Autocalibrated Relaxometry Unit (ARU**

$$\%\Delta[Fe^\star]_{act.} = \Delta R^*_{2act.}/R'_2$$

- Here we ask whether ARU is a more sensitive and specific metric of neural activity than conventional BOLD percent signal change (PSC).

## Materials and Methods

- Source ME-fMRI data in the resting-state drawn from previous studies (n=298)[34]
- Extracted signal from 10 networks derived from Human Connectome Project with 100K individuals[5]
- Evaluated and compared effect sizes of PSC and ARU
- Test-retest reliability examined across timepoints and scanner field strengths

## Large effect size of ARU across the whole brain and 10 canonical human brain networks

*ARU shows absolute quantification of resting neuronal activity localized to gray matter regions*

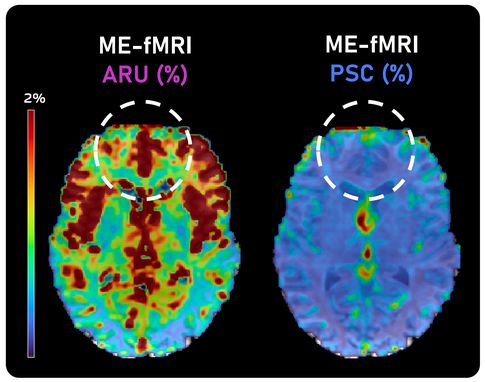
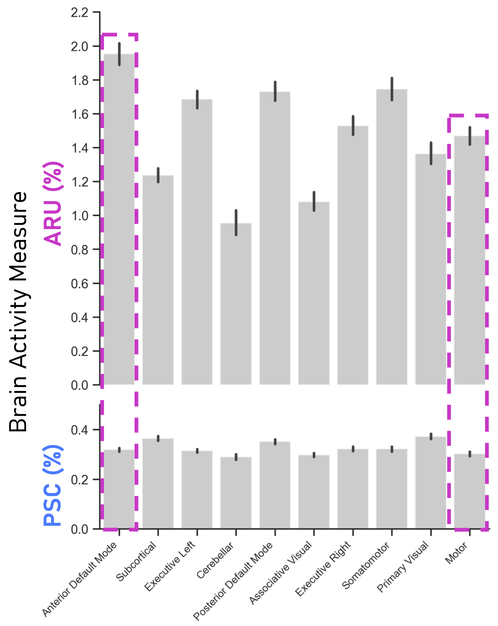



**Figure 2 |** Based on the same raw data, ARU quantification demonstrates a 4-fold increase in amplitude (%) in gray matter compared to PSC, also known as contrast-to-noise. This was found without need for additional noise regression or statistical control.

*ARU, not PSC, distinguishes activity levels across networks in predictable patterns*



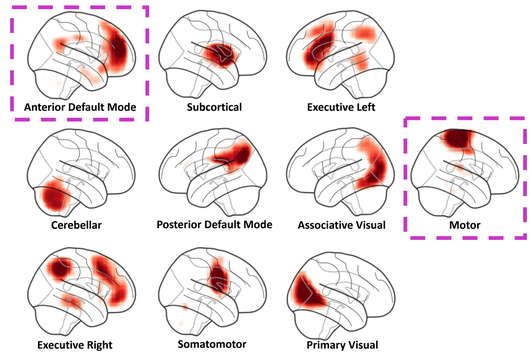




**Figure 3 |** Across the 10 functional networks examined (right), amplitude of ARU was 4 times higher than PSC. Unlike PSC, amplitude in ARU was specific to gray matter and sensitive to different networks. Measured during the resting-state, ARU was highest in the default mode network and was distinguished from the motor network, as illustrated by the purple dashed boxes.

## ARU demonstrates high test-retest reliability

*Across scanning sessions*

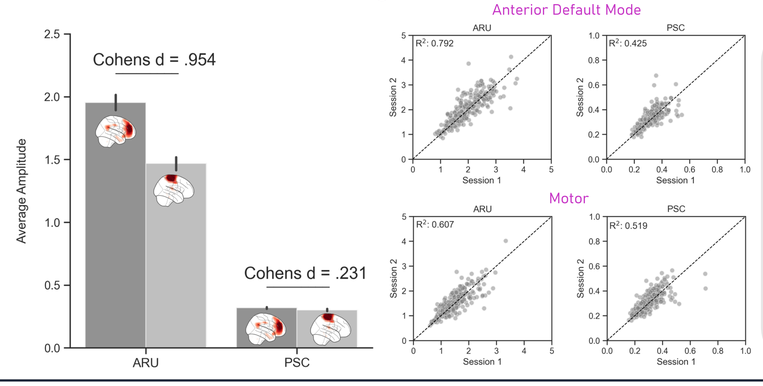



**Figure 4 |** Using the default mode and motor networks as an example comparison, ARU showed significantly higher effect size to distinguish between networks (left). Test-retest reliability was also higher across scanning sessions (right).

*Across field strengths*

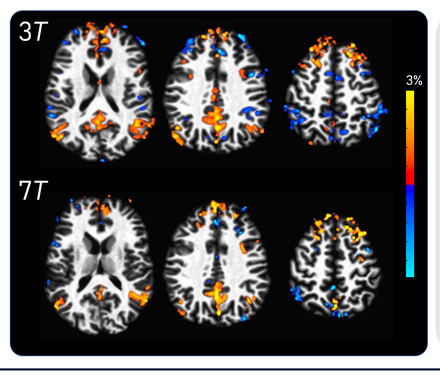



**Figure 5 |** The pattern and magnitude of neural activity in ARU is **comparable** across field strengths. PSC magnitude scales with field strength.

## Conclusions

- ARU, a novel quantitative imaging strategy based on ME-fMRI, produces a measurement unit for brain activity that has effect sizes 4 times larger than the current strategy. Using a novel physiological basis in NMR relaxometry, we link neural signal to oxyhemoglobin dynamics.
- ARU demonstrated within-network consistency and between network differentiation appropriate for the "resting state" across a heterogeneous sample of age and scanner without covariates, demonstrating autocalibration.
- **These results suggest that ARU is a suitable metric to standardize expected values of brain activity across a variety of neuropsychological domains and CNS disorders in both small and multi-site trials.**

## References

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