

Risks of Overinterpretation in Resting-State fMRI: The Threat of Noise

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Introduction

Common metrics in resting-state fMRI

- **Correlation:** cross-region synchronization in BOLD signal
 - * surrogate for neural-level relationships
 - * differences across groups or conditions
 - * potential applications: predictors for biomarkers and therapy
- **Graph metrics:** derived from graph-based analysis
 - * basic units: node/region, edge/correlation
 - * derived features: hub, node centrality, node efficiency, betweenness centrality, closeness centrality, cliques, modularity, community, ...

Critical questions

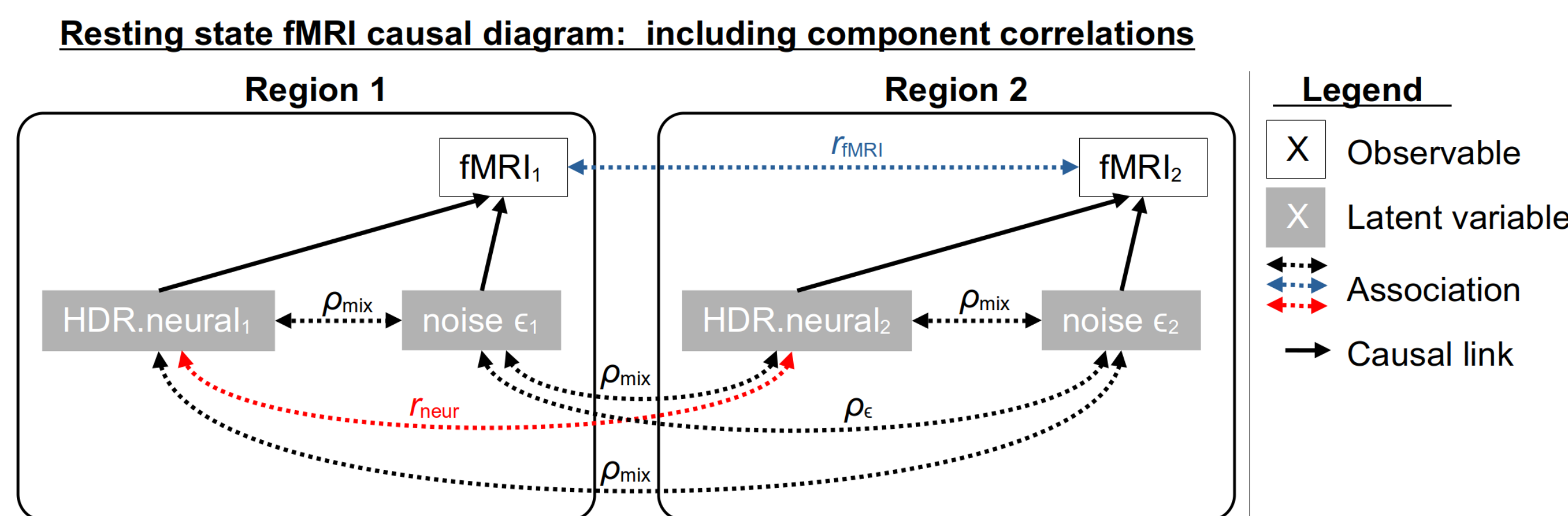
- How reliable are correlation estimates for capturing cross-regional synchrony?
- What are the consequences of inaccuracies in estimated correlations?
- To what extent do correlations reflect true neural interactions?

Noise: a big threat

- Different sources of noise
- What is the impact on estimated correlations in the presence of noise?
 - * underestimation or overestimation?
 - * how to assess the impact?

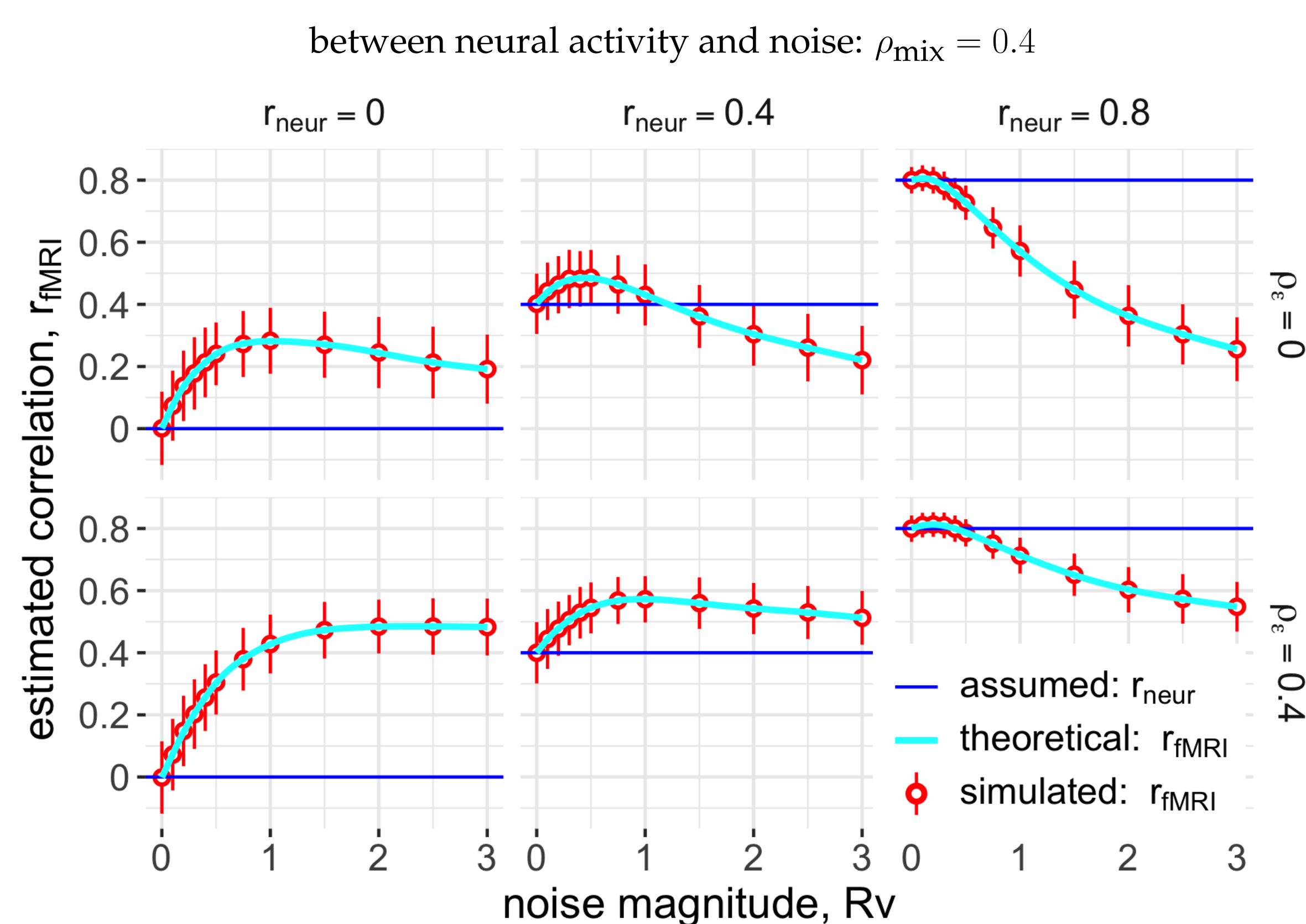
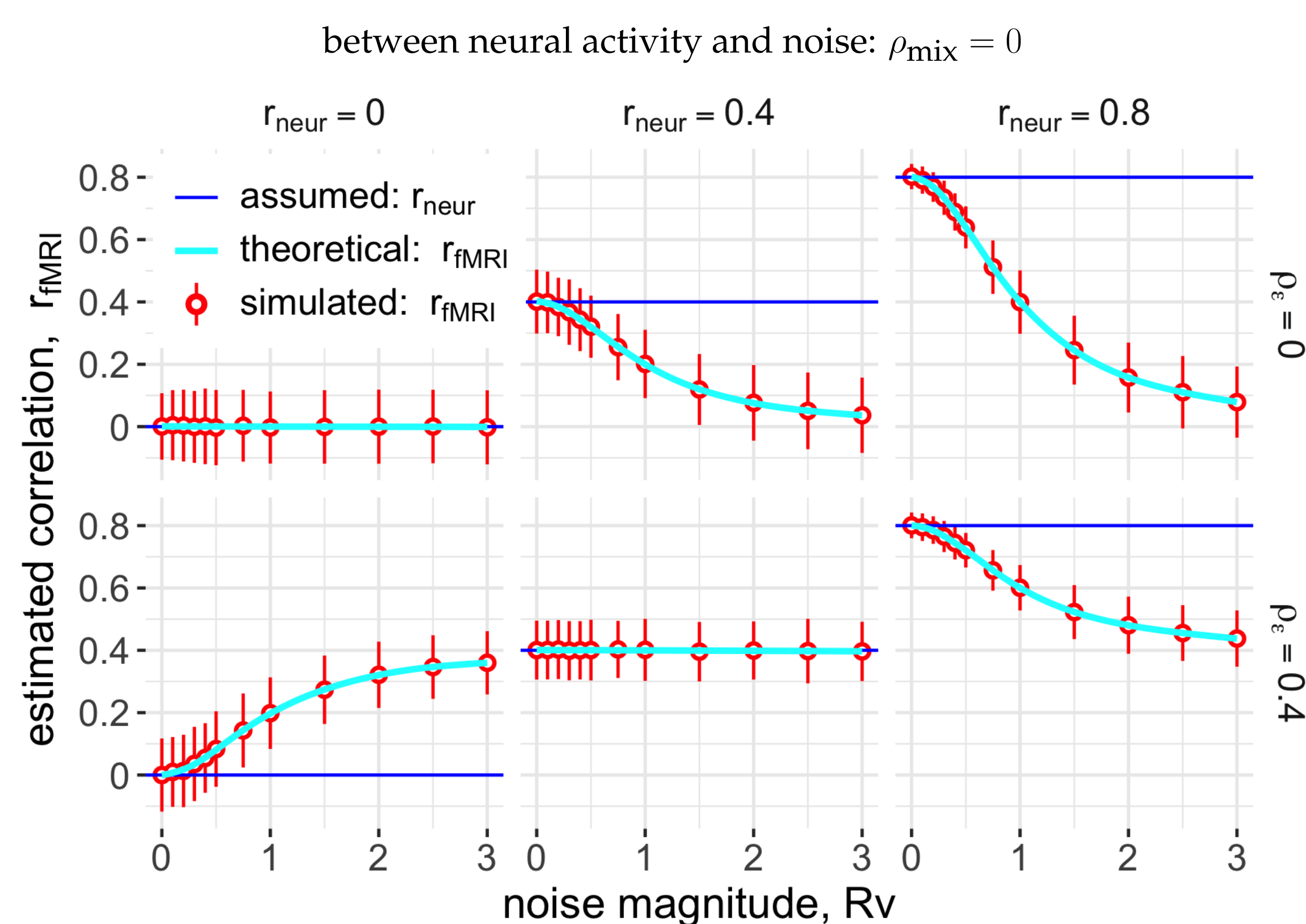
Impact of noise: complex scenarios

- Relationships between two regions: signal, noise and shared components



Simulations show the impact of noise on estimated correlations: it's complicated!

- both under- and over-estimation may occur
- biases depend on
 - * magnitude of noise relative to BOLD signal R_v
 - * correlation between neural activity and noise ρ_{mix}
 - * noise correlation between the two regions ρ_e
- no practical ways to differentiate bias direction
- bottlenecks exist in noise mitigation

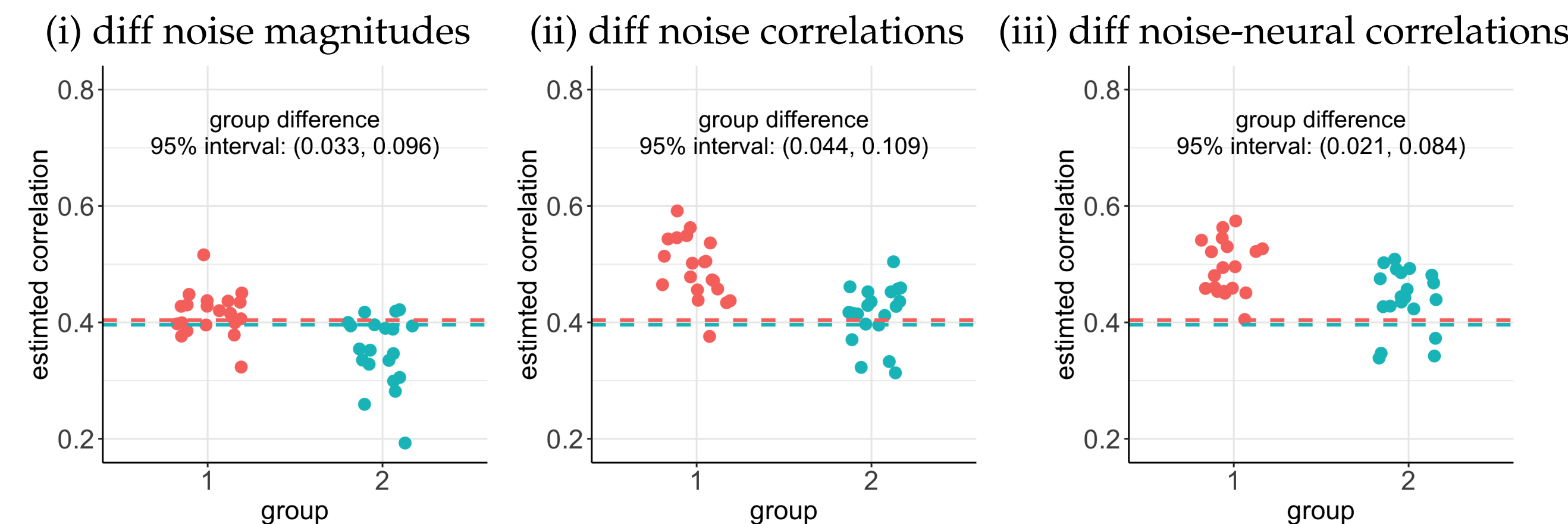


Group comparisons of correlation can be distorted in various ways:

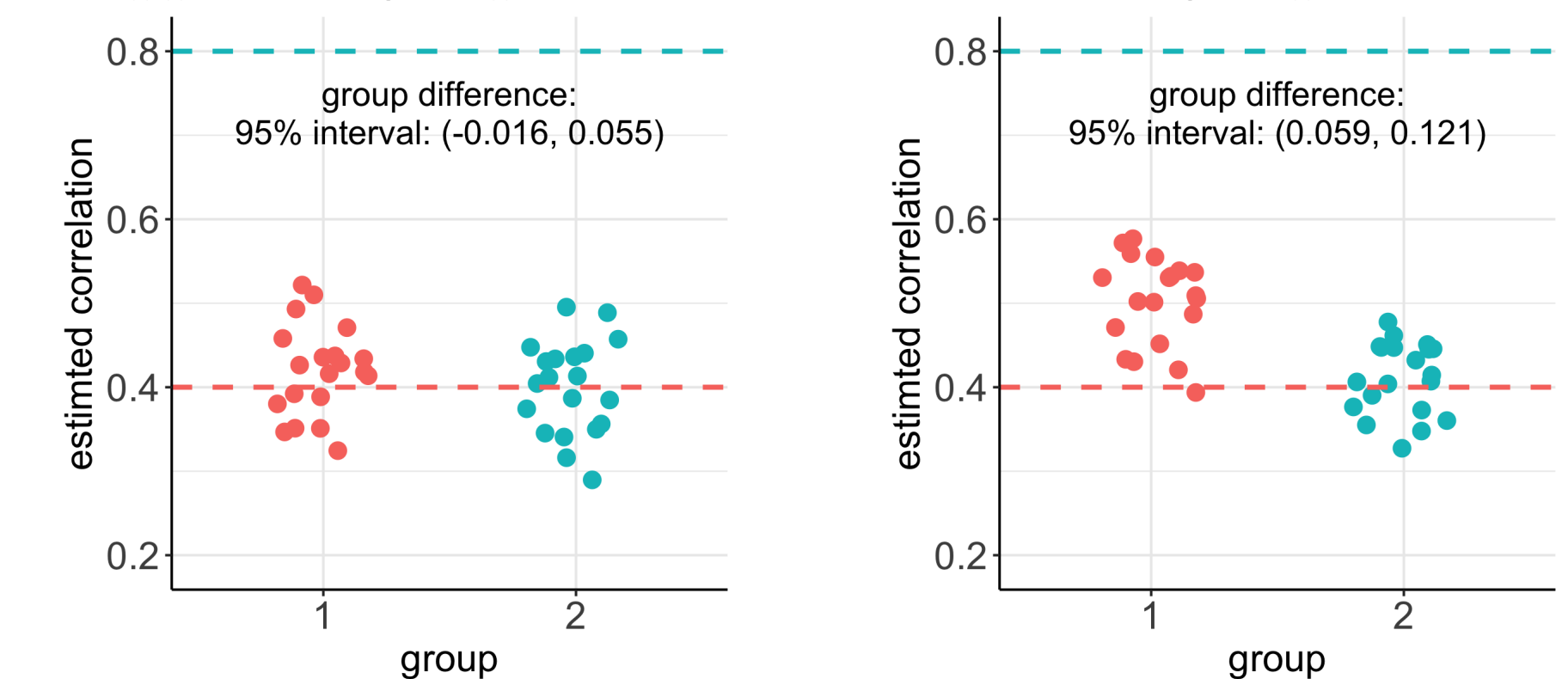
- group difference may be entirely attributed to noise
- group difference may be fully masked by noise
- group difference may be sign-flipped by noise

In the simulations results below, the dashed lines show the real, underlying average correlations for each group. Dots show the estimated correlation values for participants in each group, which can either mask similarity, hide or distort differences all due to the presence of noise.

A) Spurious group differences detected despite identical neural-level correlations ($r_{hdr} = 0.4$)



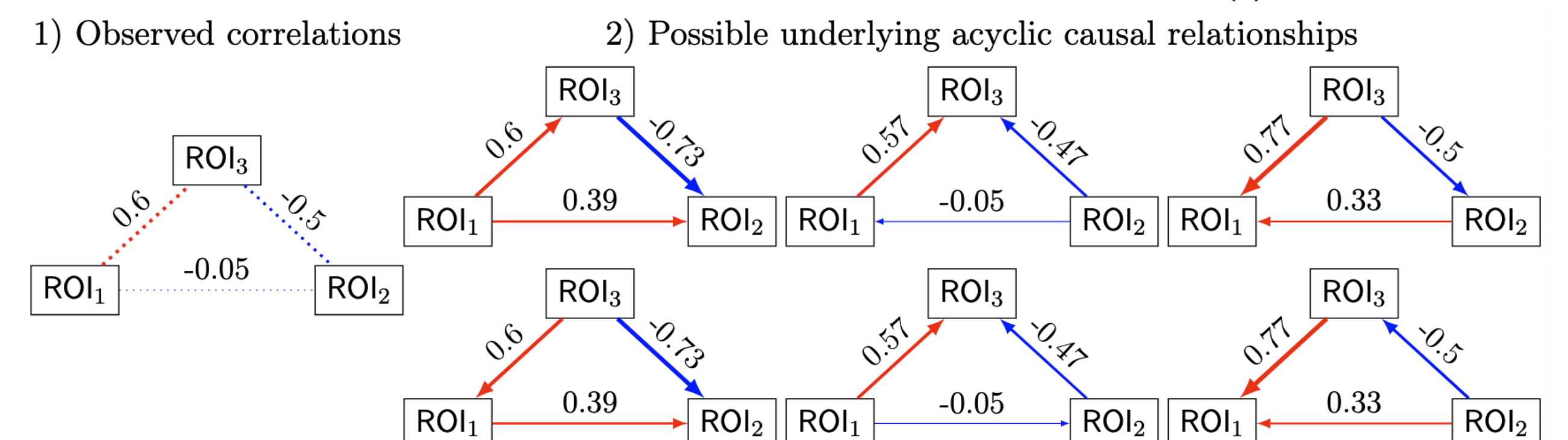
B) Suppressed group difference C) Reversed group difference



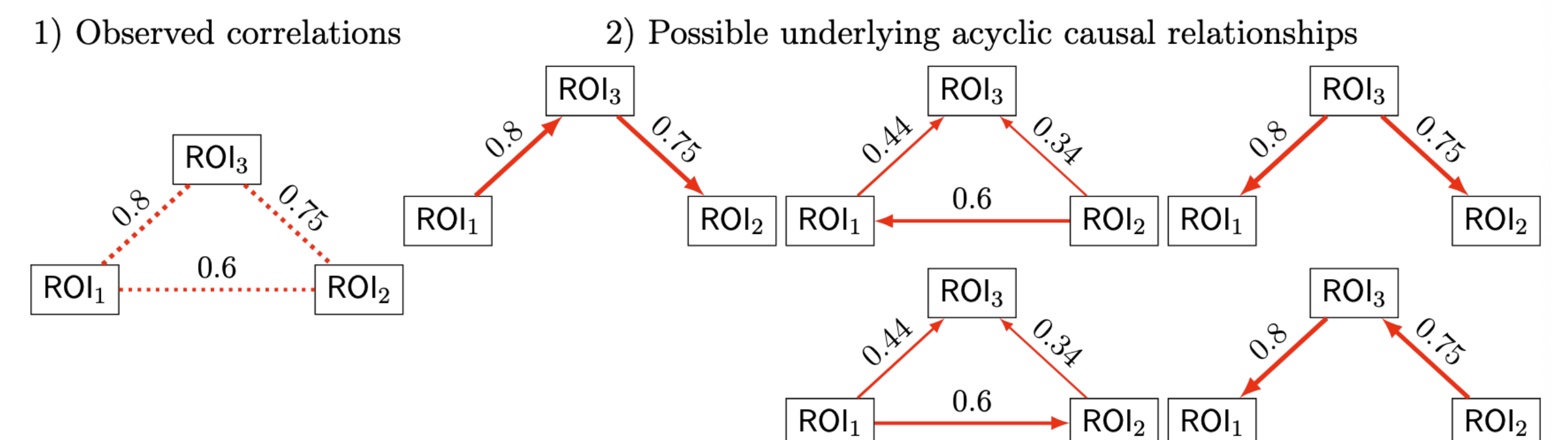
Graph features: interpretation difficulties

- **A simple scenario with 3 regions:** can we determine which connection "significant" edges?
 - A set of 3 correlations corresponds to 6 (very) different underlying causal relationships
- **Interpretation difficulties:** surprisingly, no definite yes/no to the following basic questions!
 - Does a near-zero correlation necessarily imply no information flow?
 - Does the sign of a correlation (+ or -) $\Rightarrow$ excitatory or inhibitory information flow?
 - Can magnitude of a correlation reliably infer the strength of information flow?

Case A: Correlation can have surprising causal effect(s)



Case B: Nonzero correlation can have zero causation



Graph features (node, edge, hub, etc.) face interpretation difficulties

- correlation in BOLD response: not reliable reflection of neural-level correlation
- neural-level correlation cannot disambiguate cross-region causal relationships

Conclusions

- **Noise:** big threat in resting-state fMRI correlation estimation
 - under- or over-estimation may occur, but difficult to predict
 - may cause misleading statistical inference
- **Interpretation challenges:** slippery slopes to causation
 - commonly seen in literature
 - difficulties in graph-based analysis
- **Potential improvements**
 - avoidance of overinterpretation
 - cross validations: multimodal imaging methods

References

Chen, G., Cai, Z., Taylor, P.A., 2024. Through the lens of causal inference: Decisions and pitfalls of covariate selection. *Aperture Neuro* 4. 10.52294/001c124817

Acknowledgments

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