Predicting Response to Vagus Nerve Stimulation using Static and Dynamic Models of Functional Connectivity

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At a glance:

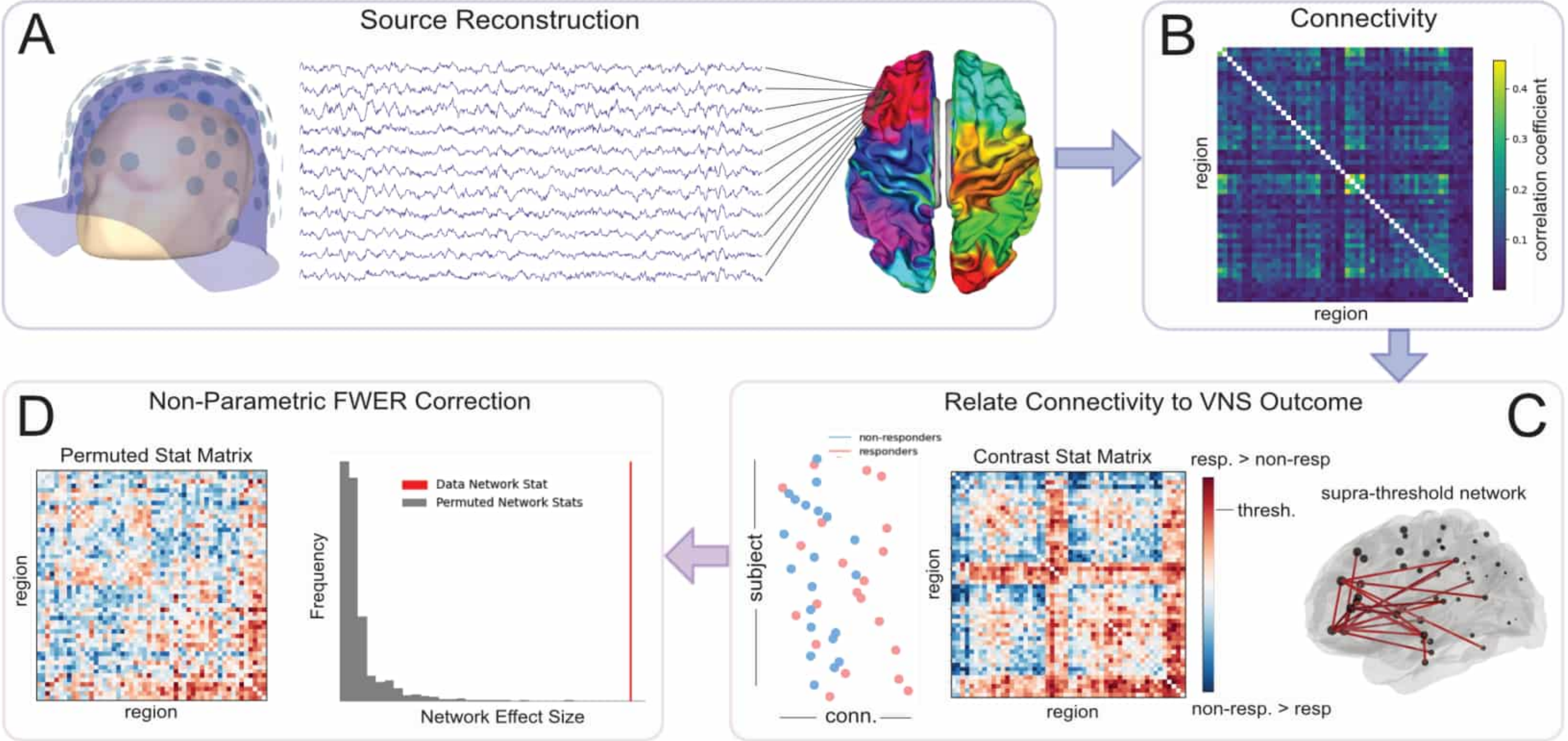
We use magnetoencephalography (MEG) to investigate seizure response to vagus nerve stimulation (VNS). We identify a network that is strongly related to VNS response, forming a promising potential biomarker. Using dynamic connectivity, we find differences between response groups in networks disrupted by interictal epileptiform discharges (IEDs).

Introduction and Aims

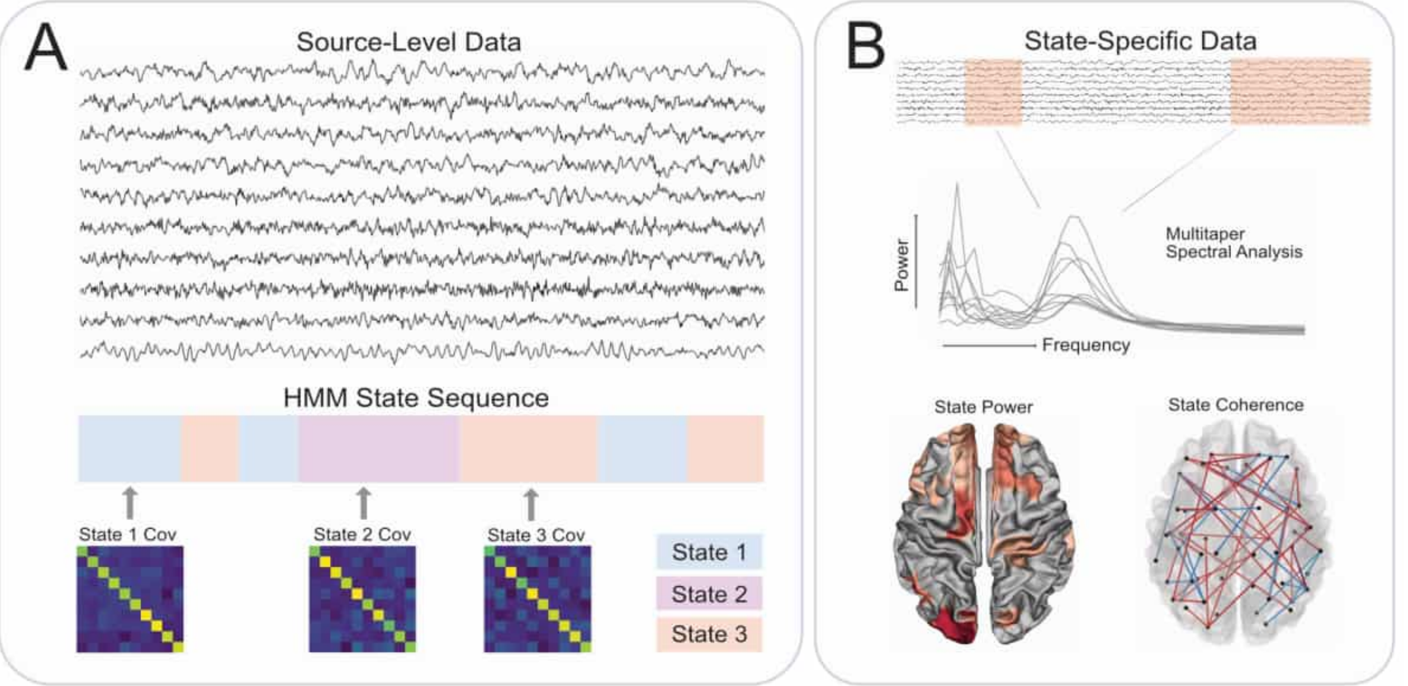
- **Vagus nerve stimulation** (VNS) is a safe and effective treatment for **drug-resistant epilepsy** (DRE) in children [1].
- **Approximately half of children do not achieve meaningful seizure reduction** (> 50%) with no clear biomarkers to guide presurgical decision-making.
- We use **magnetoencephalography** (MEG) to study **preoperative** network activity in children with DRE that underwent VNS treatment. MEG provides the optimal balance of temporal resolution, spatial specificity and whole-brain coverage.
- We first study **static MEG connectivity** to identify potetial **network biomarkers** of VNS response and non-response.
- We then use a **hidden Markov model** (HMM) to study **network dynamics** related to interictal epileptiform discharges.

Methods - Static Connectivity

- MEG data were preprocessed and **projected into 52 cortical domains** using a beamformer (**A**).
- **Connectivity** was estimated for each subject (**B**) using amplitude envelopes in canonical frequency bands.
- Connectivity was **related to VNS outcome** using t-tests (reponders vs non-responders), and the resulting statistical matrix was thresholded to form connected networks related to VNS response (**C**), each with an associated intensity score.
- Family-wise error rate (FWER) was controlled using **network-based statistics** (NBS) [2] - permuting the data and comparing the initial network intensity scores with permuted network intensities (**D**).
- Logistic regression was then used to **predict VNS outcome** using MEG connectivity, with **no prior feature selection**.

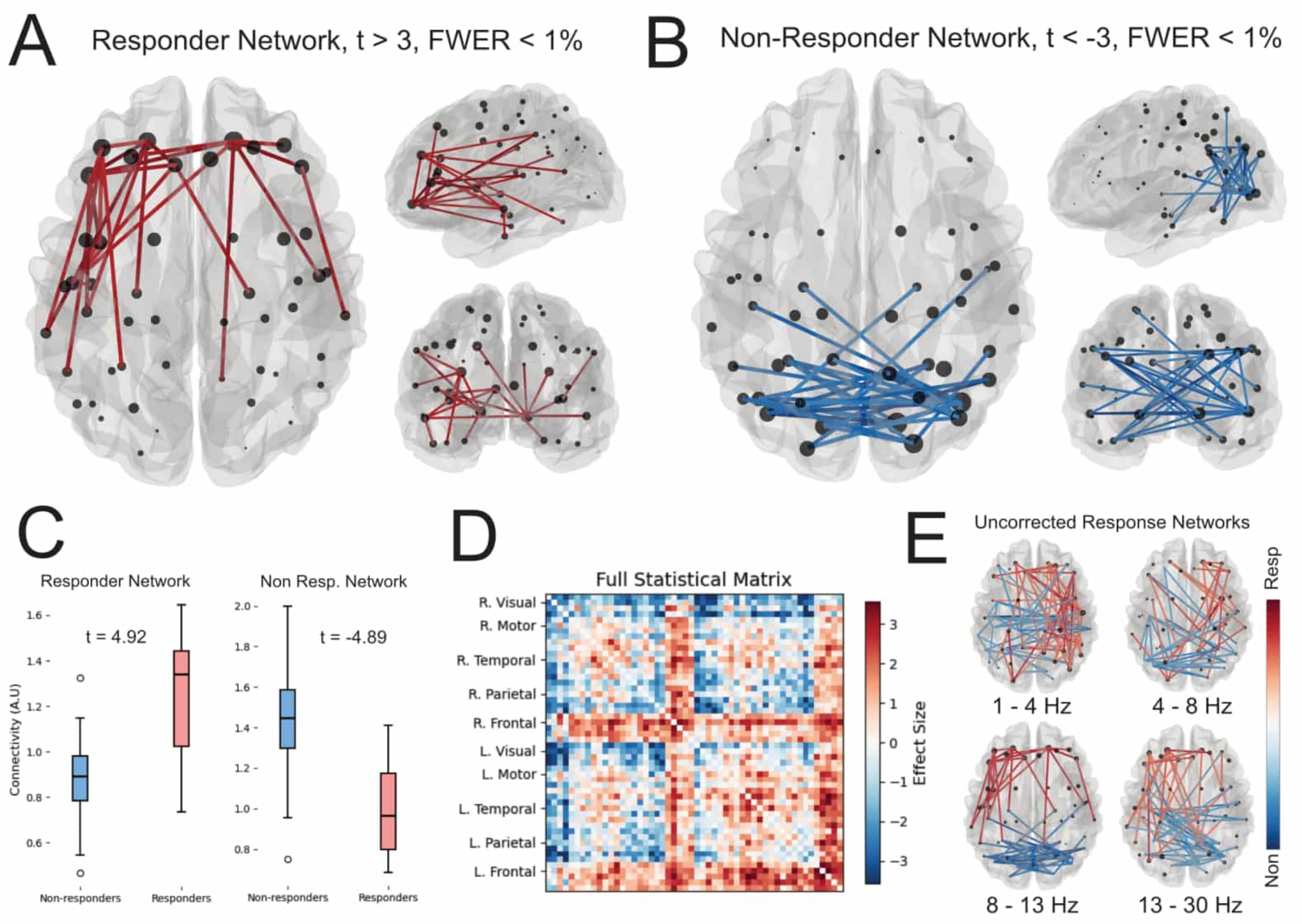


Methods - Dynamic Connectivity

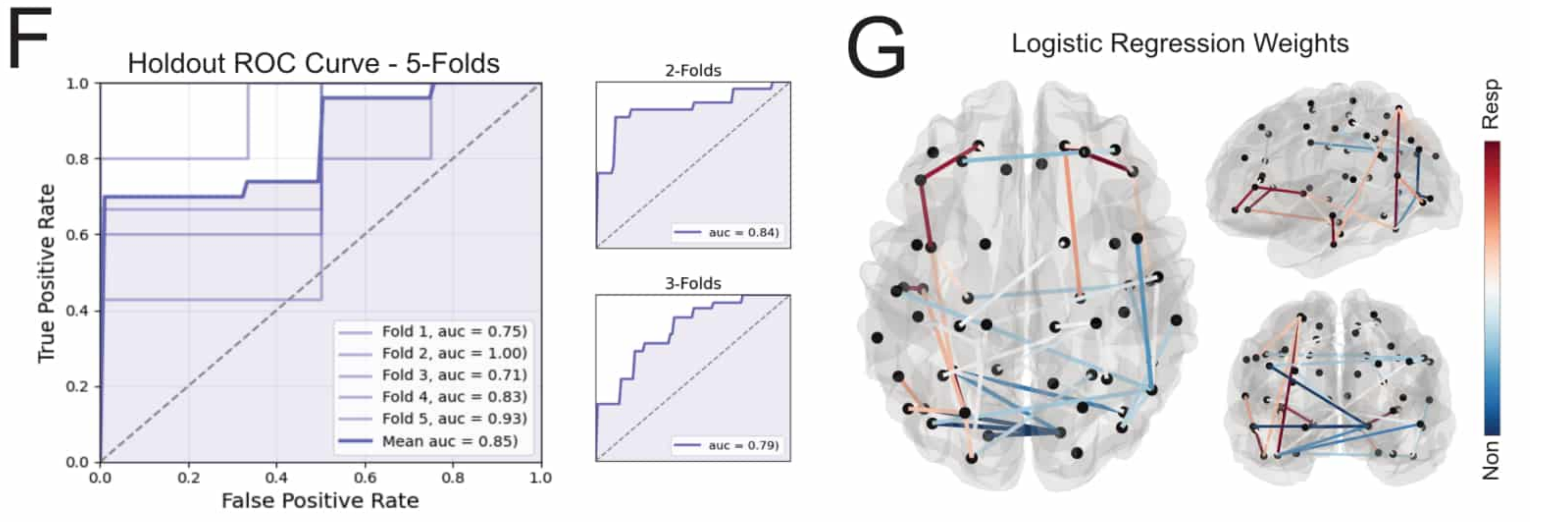


- The data were decomposed into **spatiotemporal "states"** (**A**) using an **HMM** [3].
- States that showed distinct increases in probability around interictal epileptiform discharges (IEDs) were labelled **IED-states**.
- **State-specific power and coherence** were calculated using the multitaper method in timepoints associated with each IED state (**B**), and compared across VNS response groups.

Results - Static MEG Connectivity



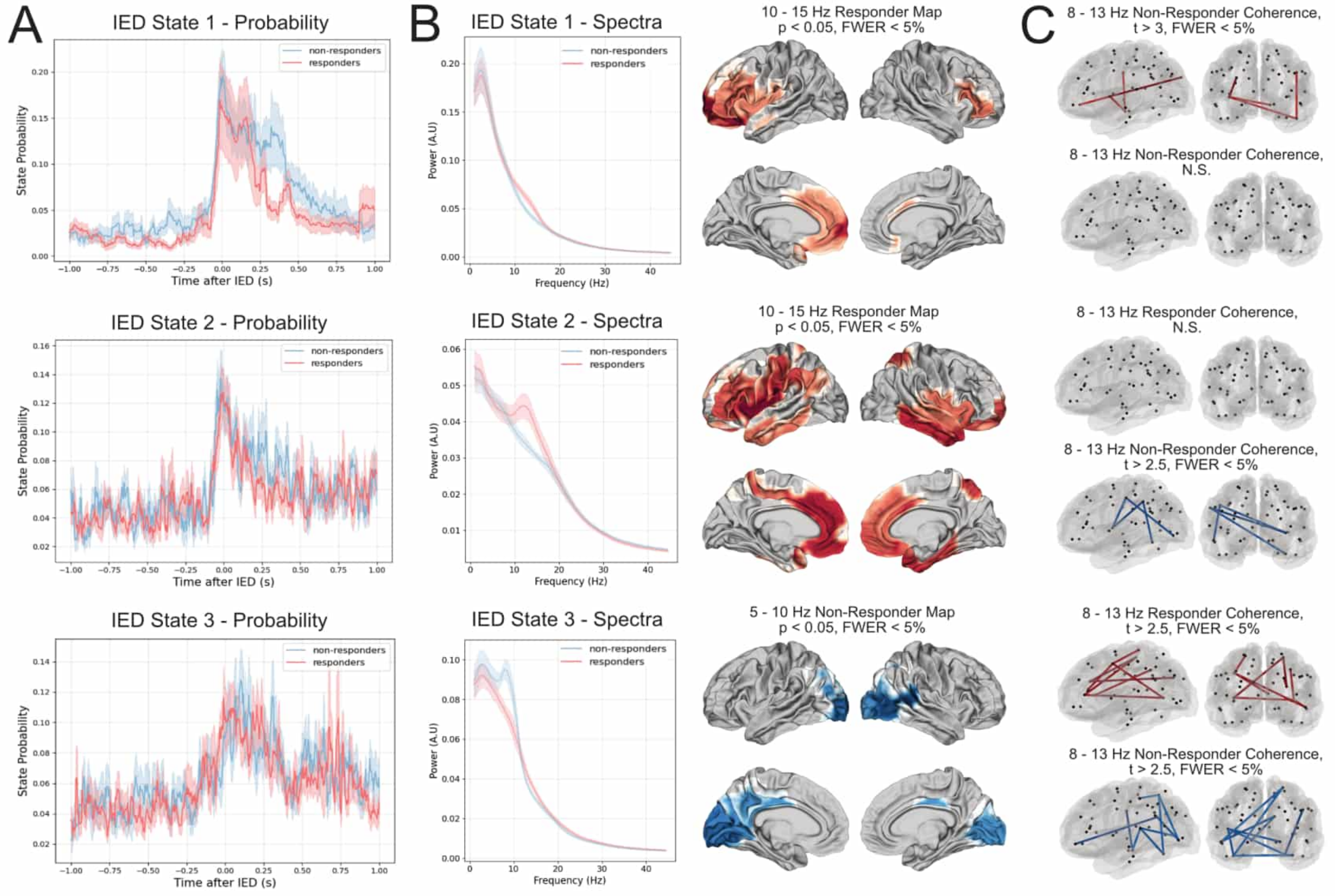
- We found **alpha-band** (8 - 13 Hz) networks that are **strongly related to VNS response** (**A**) and non-response (**B**). These networks were found by setting an initial t threshold of 3 (~ p < 0.002) and FWER controlled at 1% with 5000 permutations.
- Effect sizes within the significant networks are demonstrated in the boxplots in **C**.
- The full alpha-band statistical matrix, showing effect sizes in all pairs of regions, is shown in **D**.
- Response networks across all frequency bands tested are shown in **E**, showing similar patterns in connectivity across all bands, with highest signal-to-noise in the alpha band, likely due to highest overall power in alpha.
- This is the first time that **source-level, resting state MEG networks** have been used as an independent measure to **distinguish responders and non-responders** to VNS treatment.



- In a simultaneous, independent analysis, **MEG connectivity was able to predict VNS outcome** in a 5-fold cross validation with high accuracy (**F**, mean AUC = 0.85). Note that **none of the associative features from the previous analysis were used to inform this predictive analysis**. Regression weights are shown in **G**.
- Predictive capabilities were consistent across lower numbers of folds, signifiying **robustness** across the entire dataset.

Results - Dynamic MEG Connectivity

- We inferred 15 dynamic network states over the entire dataset using an **HMM**.
- We identified **3 IED states**, signified by a distinct **increase in probability following IEDs** (**A**). IED state probability did not differ significantly between responders and non-responders.
- Using multitaper analysis, we find that **responders** had greater 10 - 15 Hz power in IED state 1 and state 2, whereas **non-responders** had greater 5 - 10 Hz power in IED state 3.
- IED-associated increases in alpha power within **prefrontal, temporal and somatosensory networks** were identified in VNS **responders**. Conversely, **non-responders** demonstrated IED-associated increases in theta power in **visual cortices**.
- **Coherence** analysis (**C**) also shows that **different networks are perturbed** by IEDs in responders and non-responders to VNS.



Conclusions

- We provide evidence that **static MEG connectivity** can be used to **preoperatively** distinguish responders and non-responders to VNS, providing a promising biomarker.
- Epilepsy phenotypes with **baseline network activity and IED-related dynamics** in a particular network are **more likely to respond to VNS**. This network consists of orbitofrontal, prefrontal, insula, temporal and primary somatosensory nodes, highly consistent with existing theories of the **vagus afferent network** [4].
- This is the first demonstration of associations between IED-related network dynamics and neuromodulation outcomes, forming a highly translatable methodology that could be applied to other treatments for DRE.

References

[1] Clifford, H.J., et al, 2024. Vagus nerve stimulation for epilepsy: A narrative review of factors predictive of response. Epilepsia.
[2] Zalesky, A., et al, 2010. Network-based statistic: identifying differences in brain networks. Neuroimage, 53(4), pp.1197-1207.
[3] Gohil, C., et al, 2024. osl-dynamics, a toolbox for modeling fast dynamic brain activity. Elife, 12, p.RP91949.
[4] Hachem, L.D., et al, 2018. The vagus afferent network: emerging role in translational connectomics. Neurosurgical focus, 45(3), p.E2.

Acknowledgements

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