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Multi-modal data integration to relate electrophysiology to (neuro)biological foundations

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Introduction
Understanding links between (clinical) measures of brain function and their underlying molecular, synaptic constraints is essential for developing and utilizing personalised interventions. We developed a flexible approach to integrate multi-modal datasets of different spatial scales and test hypotheses on how micro-/mesoscale properties shape macroscale brain dynamics. Here, we used intracranial electro-physiological data (normative iEEG atlas, Montreal), microscale synaptic data (neurotransmitter receptor density maps, Juelich) and a hierarchical Bayesian framework (dynamic causal modelling (DCM), University College London) to explain how neuroreceptor topography shapes cortical iEEG.

Methods
This study comprises three steps. First, we employed canonical microcircuit models (CMC) to generate iEEG spectra and obtain baseline fits. Subsequently, we investigated how regional receptor compositions ('fingerprints') explain variations in cortical electrophysiology; we leveraged a flexible parametric empirical Bayesian hierarchical approach to do this. The purpose of this step was to demonstrate how multi-modal data can be integrated to evaluate hypotheses and how generative models of neural populations can be enhanced by neurobiological priors. We obtained model evidence, which was used to determine a winning model, and neurobiologically-informed connectivity parameters. Eventually, normative parameters from the winning model were used in a worked-example of mismatch negativity to demonstrate how the derived parameter posteriors can serve as priors to facilitate optimisation and hypotheses testing.

Results
Baseline fit: canonical microcircuit models generated ongoing awake cross spectral densities of iEEG signals (1770 data series) accurately; with 40 exceptions (≙ 2.3% had a mean squared error (MSE) > .05), the CMCs were able to generate key components of regional cortical signal variability.
Neuroreceptor-informed models: comparison of 21 candidate models –combinations of neuroreceptor densities and principal component informed models –led to a winning model with significantly improved model evidence compared to baseline. Thus, regional receptor composition variability explains regional variation of iEEG spectra, i.e., we could obtain improved model evidence across regions, only 1/1770 had a MSE > .5. Further, the contribution to model evidence improvements of types of receptors are shown.
Worked example: derived receptor-informed parameter priors for population connection strengths were informative for modelling mismatch negativity and lead to significantly higher model evidence and fit, and improved parameter posteriors.

Contribution
Our work contributes to bridging this explanatory gap using generative neural population models. We demonstrate an approach to integrate multimodal datasets and derive a normative cortical atlas of parameters. Additionally, we show that regional oscillatory activity measured with physiological intracranial EEG is shaped and best explained by interactions of 15 neurotransmitter receptor systems and not only by GABAergic and glutamatergic neurotransmission.
Both, the method and the derived data can be used by other researchers to either integrate other (types) of data into a principled framework or use the derived normative parameter priors for the CMC neural population model to inform there own investigations.

Outlook
This approach has wide-ranging applicability in neuroscience research; especially, since the capacity to evaluate brain (dys)function with complementary modalities at varying spatial scales increases dramatically.

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