**NeuroCluster: A Python toolbox to detect electrophysiological activations related to continuous behavioral signals using time-frequency resolved multiple regression and non-parametric cluster-based permutation testing.** NeuroCluster: A Python package to detect electrophysiological signals related to complex behaviors using time-frequency resolved multiple regression and non-parametric cluster-based permutation testing.

**# Summary**

Cognitive neurophysiology offers a novel framework for studying cognitive brain-behavior relationships by relating electrophysiological signals to complex behaviors. With the advent of new biotechnologies and neurosurgical practices, large-scale human (and animal) intracranial electrophysiological recordings are becoming widely accessible. As a result, cognitive neurophysiologists can design cognitive experiments that leverage both the spatiotemporal resolution of electrophysiological data and the complexity of continuous behavioral variables (EX CITATIONS). Analyzing these data requires sophisticated statistical methods that can interpret multidimensional neurophysiological data and dynamic, continuous behavioral variables. Classical statistical frameworks for analyzing event-related time series data are ill-equipped to manage the high dimensionality and behavioral complexity of cognitive neurophysiology studies. NeuroCluster is an open-source Python toolbox for analysis of multivariate electrophysiological data related to complex, continuous behavioral variables. NeuroCluster introduces a novel statistical approach, which uses non-parametric cluster-based permutation testing to identify time-frequency clusters of oscillatory power modulations that significantly encode time-varying, continuous behavioral variables. It also supports multivariate analyses by allowing for multiple behavioral predictors to model neural activity. NeuroCluster addresses a methodological gap in statistical approaches to relate continuous, cognitive predictors to underlying electrophysiological activity with time and frequency resolution, to determine the neurocomputational processes giving rise to complex behaviors.

**# Statement of Need**

Determining the neurocomputational processes that give rise to human cognition and generate complex behaviors is a fundamental goal of cognitive and systems neuroscience. Cognitive neurophysiologists study the neural underpinnings of latent cognitive processes by relating complex behavioral signals to electrophysiological time series data. Cognitive behavioral signals, which can reflect experimental conditions, participant actions, or underlying cognitive processes, are often continuous and vary over time, especially in human behavioral experiments. Computational cognitive models are used to operationalize unobservable cognitive processes and provide estimates of latent cognitive variables, based on participants’ behaviors (Pan et al., 2024). For instance, some cognitive models generate continuous, trial-wise value estimates, like reward prediction errors (RPEs, O’Doherty et al. (2007). Directly linking these cognitive variables to neurophysiological activity offers a dynamic way to study brain-behavior relationships. Unfortunately, the innate complexities of both cognitive behaviors and electrophysiological data (CITATION) presents a significant challenge for neuroscientists using model-based analyses to uncover the neurophysiological signatures of these processes.

NeuroCluster addresses a methodological gap in cognitive neurophysiology, by providing a novel statistical pipeline to relate continuous latent cognitive predictors to underlying electrophysiological activity, with both time and frequency resolution. Non-parametric statistical testing is the standard approach to analyze event-related time series data while controlling for multiple comparisons problems and reducing family-wise error rates (CITATIONS). However, current statistical methods are ill-equipped to interpret complex, cognitive behaviors, nor can they manage the high dimensionality of multi-region intracranial electrophysiological recordings (CITATION). Classic analysis methods relate neuronal activity to discrete behavioral categories (generally two conditions), rather than continuous, trial-by-trial behavioral measures (CITATION). Neurophysiological activity is typically aggregated by trial-type to perform a two-sample cluster-based permutation test, which tests whether the neuronal encoding patterns differ between two discrete task variables (CITATION). While two-sample permutation tests provide neurophysiological results in the time and frequency domains, they are insufficient for analyses relating neuronal activity to time-varying, continuous behavioral variables. Unfortunately, standard analysis methods capable of relating neural activity to complex, continuous variables sacrifice spectral resolution in either the time (trial-averaged signals) or frequency domains (broadband frequency-averaged signals) (CITATION). Reducing the spatiotemporal resolution of electrophysiological data hinders our ability to define distinct underlying mechanisms of cognitive processes, by eliminating either the temporal profile of a signal containing within and across-region encoding onset, duration, and latency patterns (CITATION) or eliminating the signal’s frequency-specificity, despite the widely accepted theory that oscillatory activity at different frequencies corresponds to distinct neurophysiological mechanisms (CITATION). Additionally, these approaches require neurophysiologists to define *a priori* hypotheses for relevant within-trial epochs and/or frequencies, reducing the generalizability of these analyses (CITATION). NeuroCluster addresses these shortcomings by implementing a novel statistical approach to identify significant clusters of oscillatory power modulations, with time-frequency resolution, related to trial-varying, continuous behavioral variables.

NeuroCluster is an open-source Python toolbox for identification of electrophysiological time-frequency activity related to continuous behavioral variables, using non-parametric cluster-based permutation testing (CITATION). We demonstrate our approach with human intracranial local field potentials but NeuroCluster provides functionality for all types of spatiotemporal or spectrotemporal neurophysiological measures (EEG, MEG) (CITATION) and may be applicable to phase-amplitude or phase-phase cross-frequency coupling analyses (CITATION). NeuroCluster is designed to supplement existing Python-based electrophysiological analysis toolboxes (CITATION FOOOF, MNE, eBOSC), such as MNE, which currently offers a cluster-based permutation testing approach for discrete group comparisons (mne.stats.permutation\_cluster\_test) (CITATION MNE). Additionally, NeuroCluster performs analyses with multivariate behavioral data by incorporating multiple predictors to model neural activity (CITATION?). NeuroCluster is amenable to analyses using the same statistical approach for model-based latent cognitive predictors (Pan et al., 2024, O’Doherty et al. 2007), model-free cognitive variables (CITATION), as well as continuous experimental (i.e., perceptual noise; Bang & Fleming (2018)) or behavioral (INTEROCEPTIVE?) (i.e., mood ratings; Blain & Rutledge (2020)) predictors. Our novel statistical method is applicable for numerous analysis goals; the major use cases are performing an initial exploratory analysis to generate specific hypotheses, determine data-driven temporal windows and/or frequencies of interest, or to identify regional patterns of significant clusters within and between subjects (CITATION). Future directions for NeuroCluster may implement mixed effects regressions, multifrequency cluster detection, and/or group-level analysis tools (CITATIONS). NeuroCluster addresses a methodological gap in cognitive neurophysiology by implementing a novel statistical framework to relate continuous latent cognitive predictors to underlying time-frequency resolved neurophysiological signals. Directly linking electrophysiological activity to cognitive variables is crucial to understand the neurophysiological mechanisms facilitating complex behaviors and cognition.