Measuring and Investigating Periodic and Aperiodic Neural Activity

Précis

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Overview

If I ask you to perform a simple task – for example, to remember a series of words, or navigate a virtual arena to find a treasure chest, you will tend to have variable behavior over time. If I were to record the electrical activity of your brain while you do these tasks, we would see an assortment of different patterns of activity. Some of this activity is rhythmic, waxing and waning in a (somewhat) consistent fashion, some of it is transient, showing sudden, sharp, brief deflections, and some of it has no discernable pattern at all. That is to say, the electrical activity of the brain is complex and dynamic, with multiple, time-varying features of interest, be they periodic, transient, or aperiodic. How is all this activity organized in such a way as to allow you to do this task, and how does it relate to your performance, and variability therein, on these tasks? How might these patterns be different in a person with ADHD, or dementia? These are the questions that I investigated in my dissertation.

The overarching goal of my research is to characterize and explain the functional organization of neuro-electrophysiological activity, and how this organization supports cognition and relates to clinical disorders. To do so, I started with an overview of the conceptual approaches and associated methodological strategies used to investigate the functional organization of neural activity to understand the 'ontology' of the field. This included data-driven literature analysis, using tools I developed to collect and analyze the scientific literature (Donoghue, 2019). This allowed me to survey the field to orient my work around salient and timely topics. I chose to organize my work around investigating features in neural data, specifically how to measure and interpret periodic and aperiodic components of neuro-electrophysiological data, probing what these signals reflect, and how we can use them to investigate cognition and disease.

In practice, my thesis is organized around two core pillars. In the methodological work, I drew from computer science, software development, and the emerging field of data science to develop algorithms and tools to decompose neural data into theoretically motivated and robustly estimated components of interest. In the empirical work, I drew from psychology and neuroscience, applying these measures to a series of datasets and experiments, testing hypotheses regarding the functional roles and physiological underpinnings of these features. This work has helped to elucidate new ideas about how periodic and aperiodic brain activity relate to cognition and disease.

Introduction: Periodic and Aperiodic Activity

With the development of what came to be called the 'Neuron Doctrine' (Ramón y Cajal, 1911), came a revolution in neuroscience, in which the subsequent 120 years or research have sought to have investigate how networks of physically distinct cells, using a combination of electrical and chemical signaling, make up the nervous system, ultimately underlying everything we perceive, think, or do. Since then, extensive work has characterized many aspects of the nervous system, for example, physiological structures, anatomical connectivity, and gene expression of neurons. What have been slower to emerge are integrative, functional descriptions of how this all works together. To function as it does, the mammalian brain must have powerful, flexible, and efficient mechanisms for coordinating information across multiple spatial and temporal scales. How the brain does this remains an open question.

The brain employs powerful organizational processes, that can be either reactive or directed, and that flexibly adapt to a broad range of sensory inputs and motor outputs. Understanding the functional organization of the nervous system is an important topic of investigation in basic science. It is also highly relevant to clinical work, as a multitude of disorders across psychiatry and neurology display seemingly disordered, or at least different, patterns and organizations of neural activity (Voytek & Knight, 2015). Investigating how the brain coordinates information through space and time are often investigated with the use of neural field data – electrophysiological recordings of the aggregate electrical activity across groups of neurons – including intra-cranial electrodes, such as in local field potential (LFP) or electrocorticography (ECoG), or extra-cranial recordings such as electroencephalography (EEG) or magnetoencephalography (MEG).

Analyses of neural field data are applied across many different areas of research, in order to investigate functional patterns of activity. Neuro-electrophysiological data contains both periodic activity (neural oscillations), a common topic of investigation (Buzsáki & Draguhn, 2004), and aperiodic activity (He, 2014), which has been less broadly studied, each of which have distinct interpretations. The overlap of these two aspects of the data is a source of difficulty for investigations which aim to measure and interpret the properties and dynamics of one or the other component, as methods that do not explicitly consider and measure both properties of the data are liable to conflate the two components. Despite this, many commonly employed analysis methods do not attempt to explicitly measure and separate periodic and aperiodic activity.

Periodic activity, or neural oscillations are a ubiquitous feature of brain activity and are thought to play a key role in neural functioning (Buzsáki & Draguhn, 2004), while their disruption is implicated in a broad group of psychiatric and neurological disorders (Voytek & Knight, 2015). Neural oscillations are comprised of aggregate activity across hundreds to thousands of individual neurons, reflecting primarily synaptic activity (Buzsáki et al., 2012), generated by interactions and patterns of excitation and inhibition across groups of neurons (Wang, 2010). Neural oscillations are typically investigated in bands of interest, for example as delta (0.5 - 4 Hz), theta (4 - 8 Hz), alpha (8

- 13 Hz), beta (13 - 30 Hz), and gamma (30 - 60 Hz). These neural oscillations are thought to relate to the functional organization of neural activity by aiding in information flow by flexibly aligning and misaligning oscillations between brain regions (Varela et al., 2001). These kinds of phase alignments, as they are known, have been shown to organize information flow between different areas and help form dynamic brain communication networks which aid in cognition, perception, and behavior, and may be disrupted in disease states (Voytek & Knight, 2015).

Electrophysiological field data also displays prominent aperiodic – meaning irregular, or non-periodic – activity (He, 2014). In frequency representations, this is seen as the '1/f-like' structure of neural power spectra, with exponentially decreasing power across increasing frequencies, roughly following a power-law distribution. The aperiodic component of neural power spectra has received less attention than oscillations, but emerging evidence shows that it is dynamic and changes with age, task demands, and cognitive states, and has putative physiological interpretations (Gao et al, 2017). However, relatively little work has explored the properties and interpretations of aperiodic activity, as compared to the broad literature exploring periodic activity. Where studies have investigated aperiodic activity, there is a large variability in the methods employed, and interpretations of results. Altogether, there is a currently a lack of consensus for methods, interpretations, and best practices guidelines for investigations of aperiodic activity in neural field data.

Collectively, the investigation of the functional organization of neural activity is an important domain of research, wherein such investigations often focus on periodic or evoked components of the data, with relatively little work seeking to measure and investigate concomitant aperiodic activity, that is also a dynamic and informative component of the data. This dissertation examines and explores the methodological approaches for investigating neural field data, and the assumptions they embody that may lead to conflating changes in different components of the data. In particular, it addresses the problem of appropriately measuring and interpreting the combination of aperiodic and periodic activity that is present in neuro-electrophysiological data, and then applies novel measures to explore the functional organization of neural activity and its relation to cognition and disease.

Chapter 1: Parameterizing Neural Power Spectra into Periodic and Aperiodic Components

Appears in: *Donoghue et al (2020). Nature Neuroscience.*

In this chapter, we investigated properties of neural field data, exploring how the presence and overlap of periodic and aperiodic activity and the assumptions of common analysis methods suggests that many analyses methods may be confounded. We then propose a new approach for separating and measuring periodic and aperiodic activity, using frequency domain representations of neural field data, that addresses limitations of previous methods. Specifically, we propose a novel algorithm for parameterizing neural power spectra, and validate this approach on simulated data, and demonstrate how it can be applied to real datasets.

The analysis of neural field data has developed a rich ecosystem of approaches adopted and adapted from the field of digital signal processing (DSP), with the goal of identifying and measuring components of interest, such as neural oscillations, transient events, or aperiodic activity – all of which are present and overlapping in the data. Such analyses make assumptions of the data, both in the ways they operate on the data, and in how they are typically interpreted. Though recorded as fluctuations across time, analyses of neural field data often include representing and transforming the data in the frequency domain. Mathematically, via the Fourier theorem, *any* continuous time series can be perfectly represented by a Fourier Series – as a combination of sinusoidal waveforms. This mathematical convenience has led to the widespread use of frequency-domain representations and transformations. However, and importantly, frequency domain representations do not themselves imply or demonstrate any particular property of the data. For example, computing a power spectrum of neural field data, as is commonly done, does not, by itself, demonstrate that the signal contains or is comprised of periodic activity.

Due to the combination of periodic and aperiodic activity in neural data, care must be taken to appropriately apply methods, and interpret the results accordingly. Most analyses of oscillations are conducted on canonically defined frequency bands, without consideration of the aperiodic (1/f-like) component, which compromises the accurate detection and measurement of periodic oscillations. Problematically, standard analytic approaches conflate periodic parameters (center frequency, power, bandwidth) with aperiodic ones (offset, exponent), compromising physiological interpretations (Fig. 1). To overcome the limitations of traditional narrowband analyses and to reduce inferential errors caused by conflating periodic and aperiodic features, we introduce a novel algorithm for semi-automated parameterization of neural power spectra. Notably, this algorithm requires no *a priori* specification of bands; it extracts as many oscillations as are found in the data, after controlling for the aperiodic component, allowing for more accurate measurements of neural features of interest.

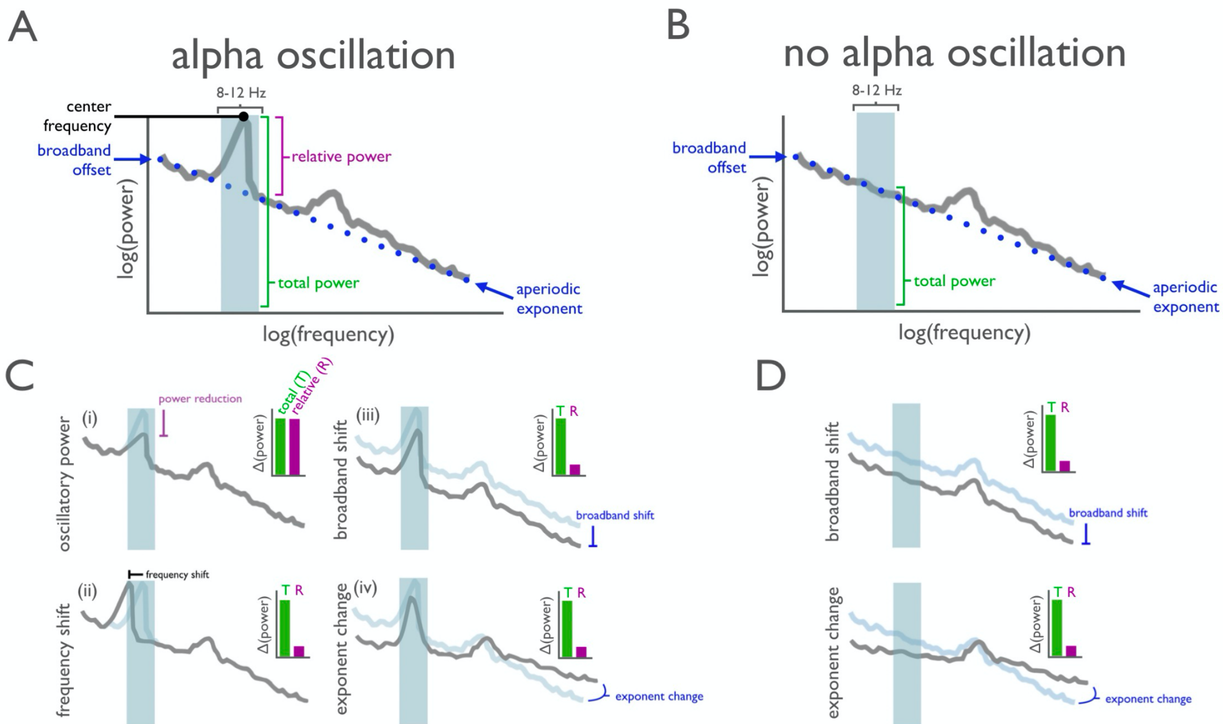

Figure 1 | Overlapping nature of periodic and aperiodic spectral features. (**A**) Example neural power spectrum with a strong alpha peak in the canonical frequency range (8-12 Hz, blue shaded region) and secondary beta peak (not marked). (**B**) Same as **A**, but with the alpha peak removed. (**C-D**) Apparent changes in a narrowband range (blue shaded region) can reflect several different physiological processes. Total power (green bars in the inset) reflects the total power in the range, and relative power (purple bars in the insets) reflect relative power of the peak, over and above the aperiodic component. (**C**) Measured changes, with a peak present, including: (i) oscillatory power reduction; (ii) oscillation center frequency shift; (iii) broadband power shift, or; (iv) aperiodic exponent change. In each simulated case, *total* measured narrowband power is similarly changed (inset, green bar), while only in the true power reduction case (i) has the 8-12 Hz oscillatory power *relative to* the aperiodic component actually changed (inset, purple bar). (**D**) Measured changes, with no peak present. This demonstrates how changes in the aperiodic component can be erroneously interpreted as changes in oscillation power when only focusing on a narrow band of interest.

Spectral parameterization (`specparam` - formerly 'fooof') parameterizes periodic and aperiodic components from neural power spectra (Fig. 2). Our approach is motivated by explicit considerations of model selection and comparison to parameterize neural data – including the physiologically motivated conceptualization of the data as reflecting a combination of periodic and aperiodic activity, and within this, explicit model comparison to evaluate the form of the aperiodic component and the number of periodic components. With this, we can compute data-driven and physiologically informed decompositions of the data, by parameterizing neural power spectra as a combination of the aperiodic component and putative periodic oscillatory peaks. To test this method, we developed a simulation platform for neural data (Cole et al, 2019). Systematic method evaluations and comparisons demonstrate that this method reliably captures ground truth and robustly outperforms other available methods.

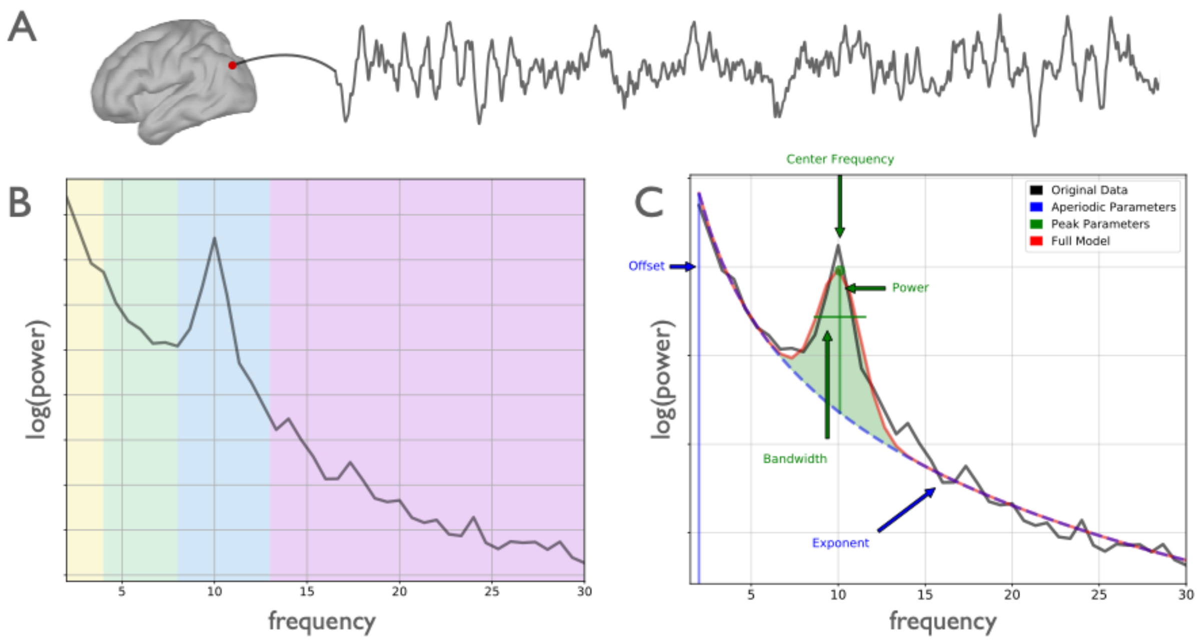

Figure 2 | Overview of the parameterization method. (**A**) Example of a (simulated) time series of electrical activity recorded from the cortex. (**B**) The power spectrum of the data in A, with shading indicating pre-defined oscillation bands, including delta (2-4 Hz - shown in yellow), theta (4-8 Hz - green), alpha (8-13 Hz - blue), and beta (13-30 Hz - purple). (**C**) The same power spectrum as B, parameterized for periodic and aperiodic activity. Each parameter identified and quantified by the parameterization is labelled. Each identified peak is parameterized by its center frequency, aperiodic adjusted power (power over and above the aperiodic component), and bandwidth. Note that peaks are detected without applying any predefined frequency regions of interests. The aperiodic component is parameterized by the 'offset', or global broadband power, and the 'exponent', which is the value of χ in $1/f^{\chi}$, which reflects the pattern of power across frequencies. For this spectrum, the algorithm identifies a peak of activity in the alpha band, whereas activity in all other bands is explained by the aperiodic component. The simulated data was simulated as a bursty alpha oscillation with a 10 Hz center frequency, over aperiodic activity with an exponent of 1.75 a.u. The measured parameters from the algorithm are a peak with a center frequency of 10.1 Hz, and aperiodic exponent of 1.76 a.u.

The spectral parameterization method is available as an open-source, easily installable, and robustly tested Python package. A marker of the utility of this approach is the level of impact it is already achieving, with over 100,000 total downloads of the Python tool. We also developed dedicated documentation (https://specparam-tools.github.io/), which, as of the end of 2021, averages 200 visitors a week, and is growing steadily, as well as the numerous invited presentations at conferences, individual labs, and to private companies that this tool has led to. There are now dozens of demonstrations of productive uses of our tool, with over 170 citations in 2021 alone from a broad range of fields and contexts. Collectively, the discussion and adoption of this tool helps to motivate that it offers a productive solution to a relevant problem in the field.

Chapter 2: Frequency Band Ratios Conflate Periodic and Aperiodic Neural Activity

Appears in: *Donoghue, Dominguez, & Voytek (2020). eNeuro.*

In this chapter, we systematically explored how spectral parameterization compares to canonical approaches, focusing on the example of frequency band ratio measures. Band ratio measures, computed as the ratio of power between two frequency bands, are a common analysis measure in neuro-electrophysiological recordings. To characterize and demonstrate the empirical application of band ratios, we used an automated literature analysis to explore the usage of such measures, and where they are typically applied. We find that that these measures are broadly used, and are particularly common in developmental and clinical applications (Fig. 3 A-B).

Notably, band ratio measures are typically interpreted as reflecting quantitative measures of periodic, or oscillatory, activity. This assumes that the measure reflects relative powers of distinct periodic components that are well captured by predefined frequency ranges. However, electrophysiological signals also contain aperiodic activity, which contributes power across all frequencies. Here, we investigate whether band ratio measures truly reflect oscillatory power differences. We first investigated, in simulation, how band ratio measures relate to changes in multiple spectral features, and show how multiple periodic and aperiodic features influence band ratio measures. We find that since such measures analyze pre-defined frequency ranges without considering and separating aperiodic activity, they are confounded by aperiodic activity as well as by other periodic changes—such as in center frequency or bandwidth—and/or aperiodic activity.

We then validated these findings in human electroencephalography (EEG) data, comparing band ratio measures to parameterizations of power spectral features, and find that multiple disparate features influence ratio measures in empirical data. For example, the commonly applied theta / beta ratio is most reflective of differences in aperiodic activity, and not oscillatory theta or beta power (Fig. 3 D-F), which substantially changes its typical interpretation. Overall, we find that commonly reported changes in periodic features are systematically confounded by aperiodic activity. In aging, for example, we find that it is aperiodic activity that is most related to age-related changes. This suggests a re-interpretation of previous work, which has typically reported this change as shifts in periodic activity with age. With collaborators, we also examined this issue in clinical work, showing that in attention deficit hyperactivity disorder (ADHD), for which the theta-beta ratio is a common analysis method that is interpreted as reflecting periodic activity, spectral parameterization demonstrates that it is the aperiodic component that most relates to clinical diagnoses (Robertson et al, 2019).

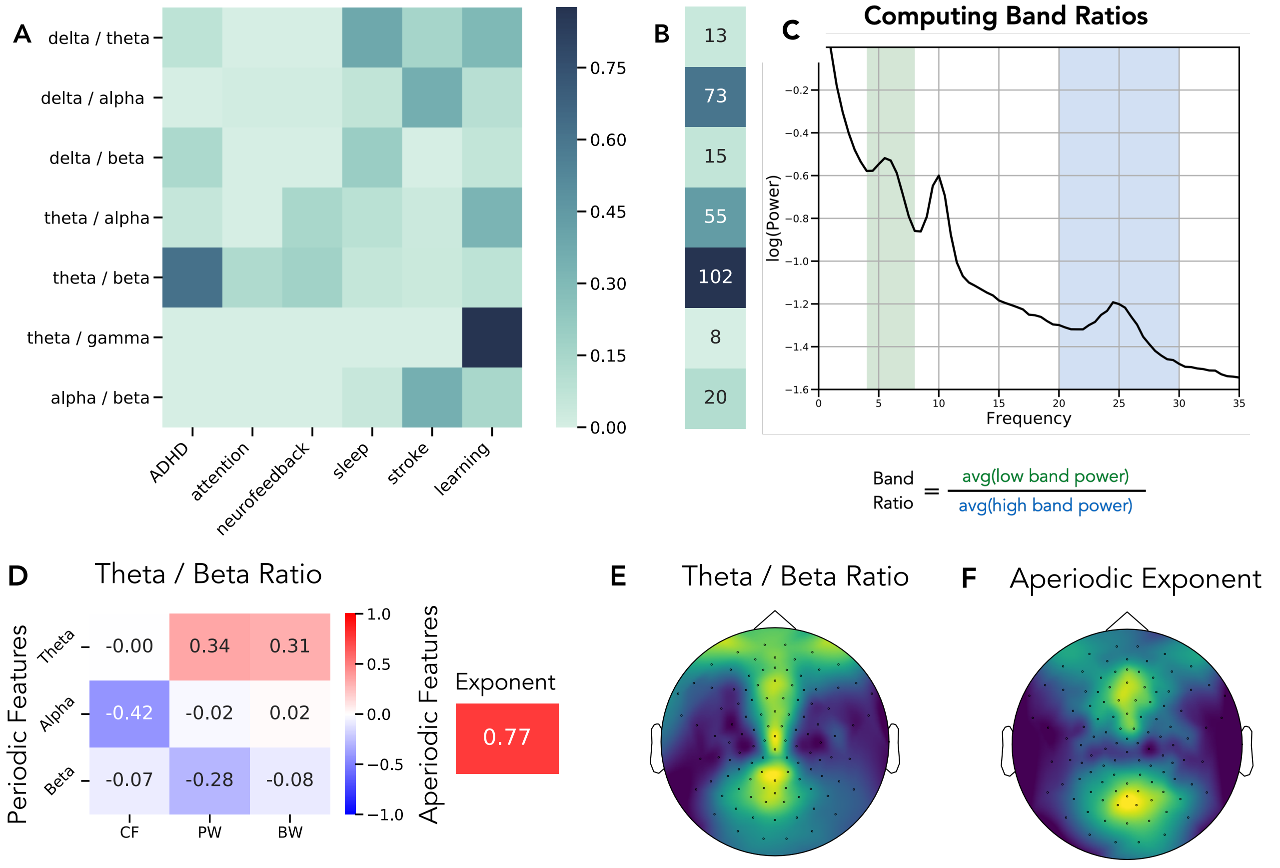

Figure 3 | Electrophysiological Band Ratio Measures. A) Associations between published journal articles referring to band ratio measures and cognitive and clinical associations. Each cell represents the proportion of articles referring to a specified band ratio measure that also mentions the corresponding association term. **B)** Total counts of the number of articles mentioning each band ratio measure. **C)** An example power spectrum in which shaded regions reflect the theta (4-8 Hz) and beta band (20-30 Hz) respectively. Band ratio measures, such as the theta / beta ratio are calculated by dividing the average power between these two bands. **D)** Correlations between spectral parameters and band ratios measures in EEG data, for the theta / beta ratio, showing that the ratio measure is most highly associated with the aperiodic exponent. Topographies of the theta / beta ratio **(E)** and aperiodic exponent **(F)** show how measures of these features overlap.

Collectively, we show that variation in periodic and aperiodic features can lead to the same observed changes in band ratio measures, and that this is inconsistent with their typical interpretations as specific measures of periodic power. We conclude that band ratio measures are a non-specific measure, conflating multiple possible underlying spectral changes, with implications to research in developmental and clinical work that have used these measures. Instead of band ratio measures, we recommend explicit parameterization of neural power spectra as a more reliable approach.

Chapter 3: Variability of Periodic and Aperiodic Electrophysiological Activity across the Human Cortex

In this chapter, we systematically explore the properties and variability of periodic and aperiodic activity across the human cortex. Both periodic (oscillatory) and aperiodic (1/f-like) activity have been implicated in healthy brain functioning and disease states, and display significant variation both within and between subjects. However, there are some limitations to prior work investigating the variability of periodic and aperiodic neural activity, including that i) many common analyses approaches do not explicitly separate periodic and aperiodic activity, and thus potentially conflate these two distinct components ii) periodic activity is typically examined using pre-defined frequency bands that may not accurately reflect oscillation occurrence and frequency variation, and iii) concomitant variability in aperiodic neural activity is rarely considered and analyzed.

To address these limitations, we apply the spectral parameterization approach to characterize periodic and aperiodic activity from neural power spectra. We apply this approach across several EEG and MEG datasets, and report on patterns of within and between subject variability (Fig. 4), noting, for example: i) between subject variability in the occurrence, center frequency, aperiodic-adjusted power and bandwidth of neural oscillations, ii) within subject topographical variability of periodic activity iii) between subject variability of aperiodic activity, and iv) within subject variability of aperiodic activity, whereby aperiodic activity varies systematically across the cortex as well as between task and rest states. In doing so, we replicated patterns of periodic activity, and quantified the large degree of variability of both features, presenting a detailed overview of within and between subject variation in neural field data, much of which may be missed by common analysis approaches. In doing so, we also validated the applicability of spectral parameterization to large-scale data exploration and analysis.

An application of interest is within aging and development, in which there is long history investigating how patterns of putative oscillatory activity systematically change over the lifespan. We investigated the hypothesis that age-related changes in neuro-electrophysiological data could be potentially better explained by variation in aperiodic components, a hypothesis suggested by the investigation of band-ratio measures. We again demonstrated in empirical data that this is the case – with systematic variation in aperiodic activity explaining the majority of age-related variance in the data – replicated in our own work, and with external collaborators (He, Donoghue et al, 2019). There are already a substantial number of related follow ups, such that we have developed a dedicated tutorial for applying spectral parameterization to developmental data (Ostlund, Donoghue, et al, 2021).

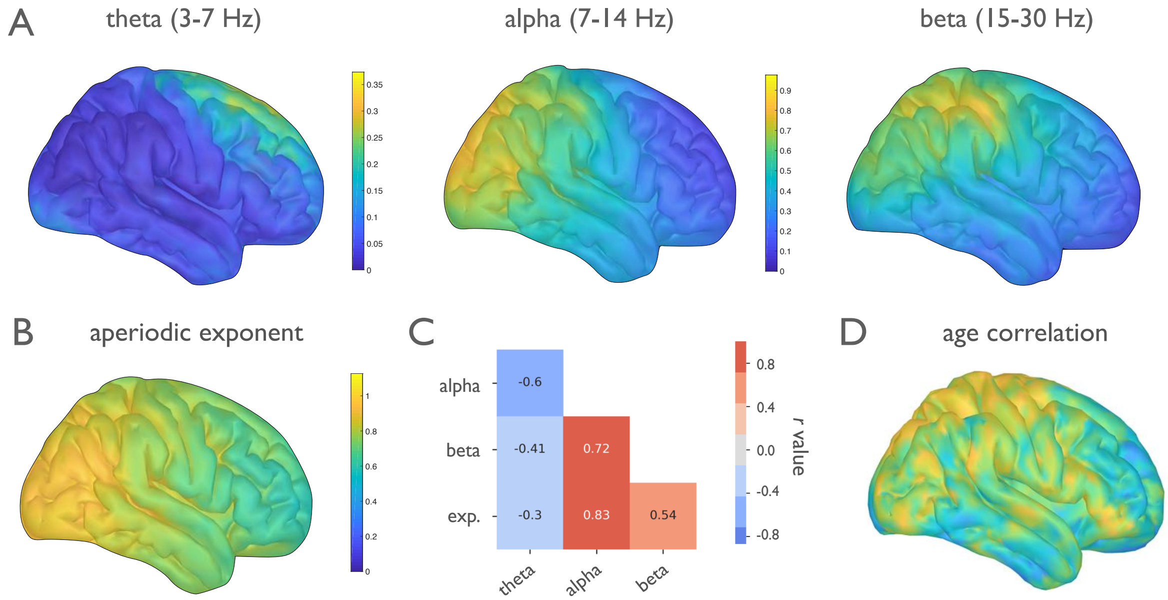

Figure 4 | Topographies of spectral features. (**A**) Oscillation topographies reflecting the oscillation score: the probability of observing an oscillation in the particular frequency band, weighted by relative band power, after adjusting for the aperiodic component. These topographies quantify the known qualitative spatial distribution for canonical oscillation bands theta (3-7 Hz), alpha (7-14 Hz), and beta (15-30 Hz). (**B**) The topography of the average (mean) resting state aperiodic exponent across the cortex, showing that the aperiodic exponent is lower (flatter) in more anterior cortical regions. (**C**) Correlations between the oscillation topographies and the exponent topography. (**D**) Correlation of aperiodic exponent to age, across vertices, showing higher magnitude correlation values in central areas. Across all locations, the aperiodic exponent showed a significant negative correlation with age ($r=-0.46$, $p<1\times10^{-4}$).

In addition, we applied spectral parameterization to task-related data, to investigate the neural correlates of cognitive behaviors. When analyzing a working memory task, we found that we can both replicate prior results suggesting alpha oscillations relate to this task, and highlight a novel association between aperiodic neural activity and task-performance (Donoghue et al, 2020). In addition, in a novel multi-sensory detection task, we have shown that aperiodic neural activity is modulated by both bottom-up and top-down processing, whereby stimulus statistics and attentional demands both independently influence aperiodic activity in a trial-by-trial manner (Waschke, Donoghue et al, 2021), suggesting a role for aperiodic activity in perceptual and attentional processes.

In sum, this work motivates that both periodic and aperiodic activity are dynamic components, necessitating dedicated methods to appropriately measure and interpret changes in the data. In doing so, methods that do consider both aperiodic and periodic activity allow for better quantifications of brain activity that can be investigated for their putative relationships to demographics and cognitive behaviors.

Conclusion

In this dissertation, we examined potential pitfalls of using methods to analyze neural field data that do not explicitly consider and measure both periodic (oscillatory) and aperiodic activity. After evaluating common conceptualizations of the data, and the implicit assumptions embodied by the methods that we employ, this thesis proposes and motivates a novel method for parameterizing neural power spectra to decompose neural power spectra into constituent components of aperiodic and periodic activity. This method was developed and validated through combining detailed conceptual, computational, and empirical work, and the algorithm is now available as an open-source tool. Through a series of demonstrations, we show that this is a productive method for investigating properties of the brain, across developmental, cognitive, and clinical contexts. Future work should continue to investigate, interpret, and understand patterns of brain activity, and how they relate to the functional organization of brain activity. In particular, while periodic neural activity remains an important feature of interest, dynamic aperiodic neural activity offers an exciting new avenue to investigate how these seemingly random patterns of activity may reflect important organizational properties of neural activity, in order to investigate the functional organization of brain activity and how it relates to cognition and disease.

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