University of
Pittsburgh

Underlying Brain Mechanisms of the Excitatory Inhibitory Balance through Adolescent Cognitive Maturation

Shane McKeon, B.S.E

Thesis Proposal

May 4, 2023

Advisor

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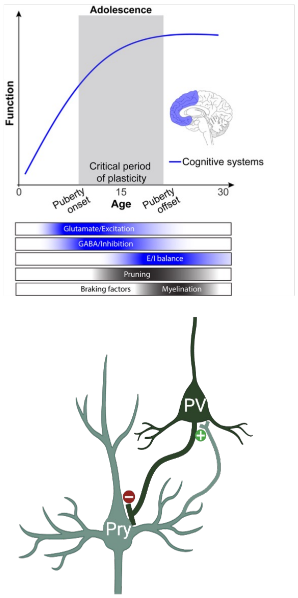
Committee

Dr. Finnegan Calabro, Dr. Taylor Abel,
Dr. Cecile Ladouceur, & Dr. Raj Gandhi

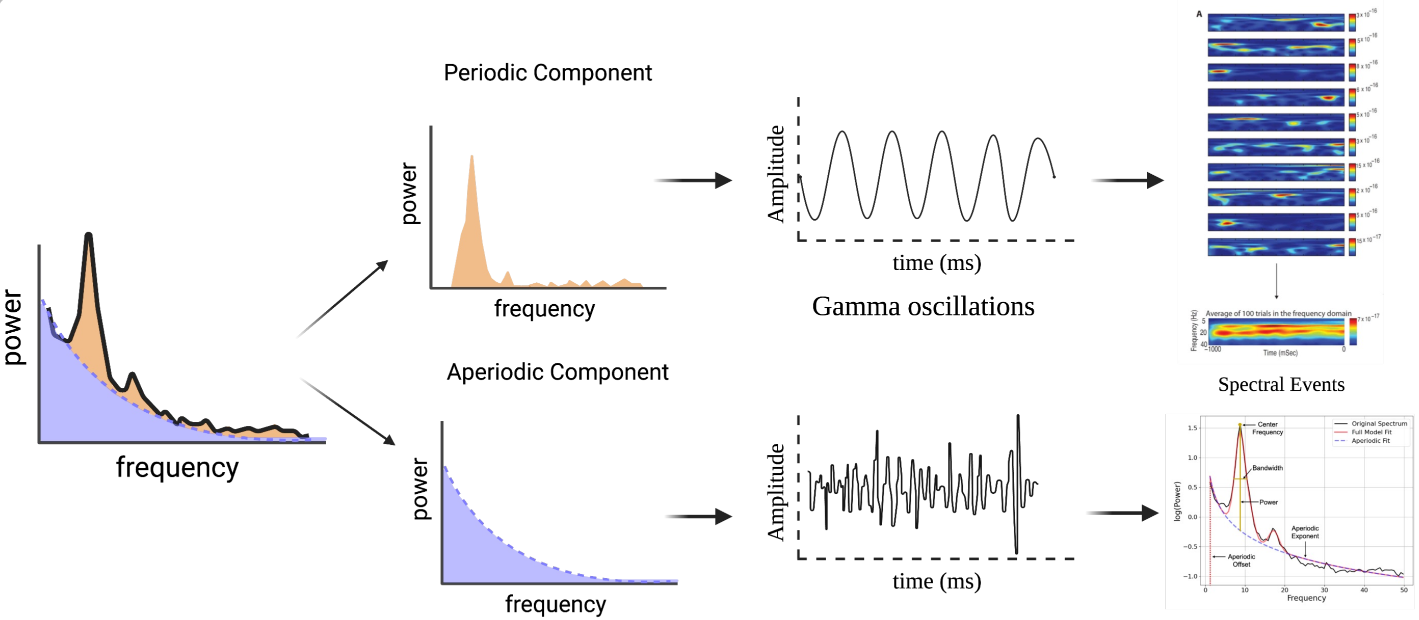
What are the underlying mechanisms of the excitation/ inhibition balance that supports cognitive maturation in adolescence?

Introduction

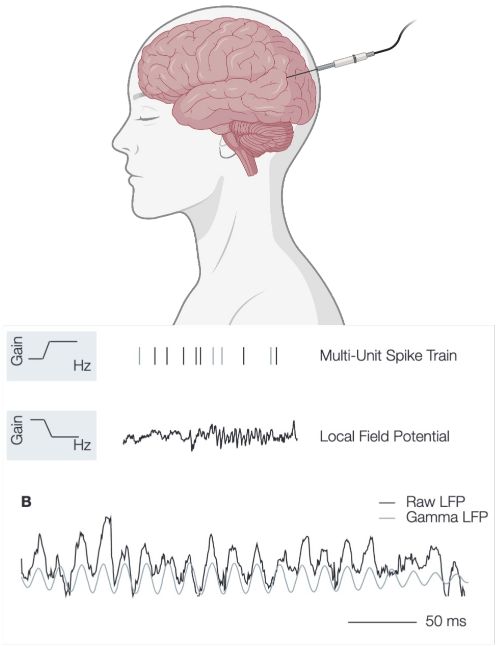


PV+ PN Circuitry

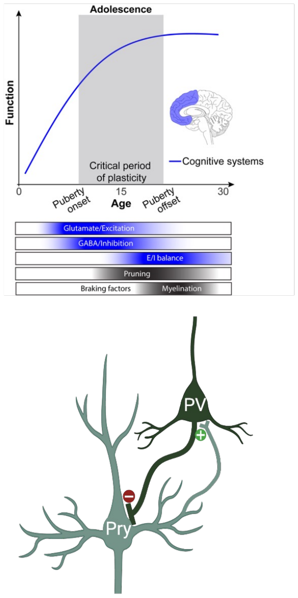
Aim 1 & 2



Aim 3



Introduction



PV+ PN Circuitry

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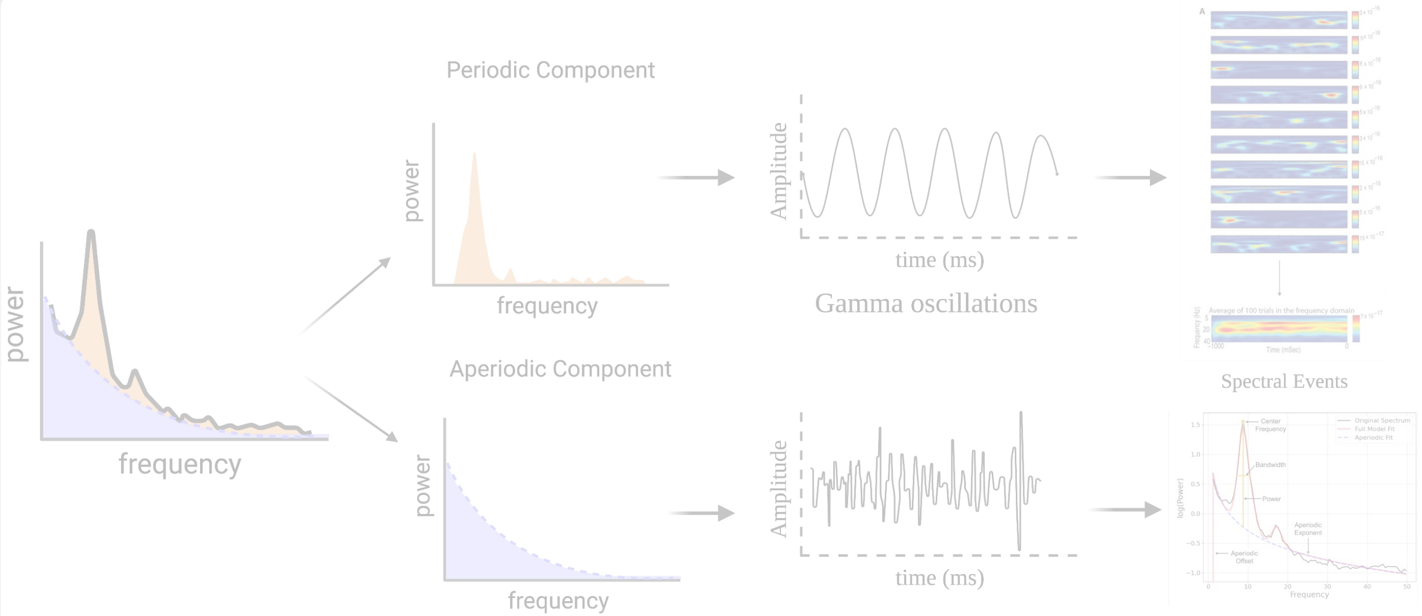

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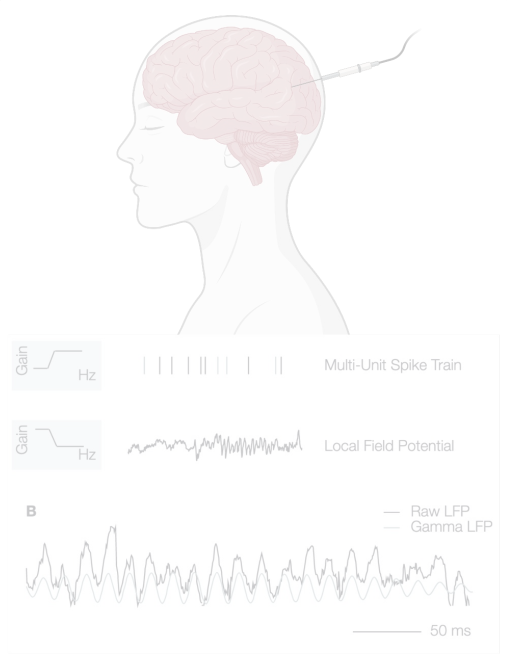
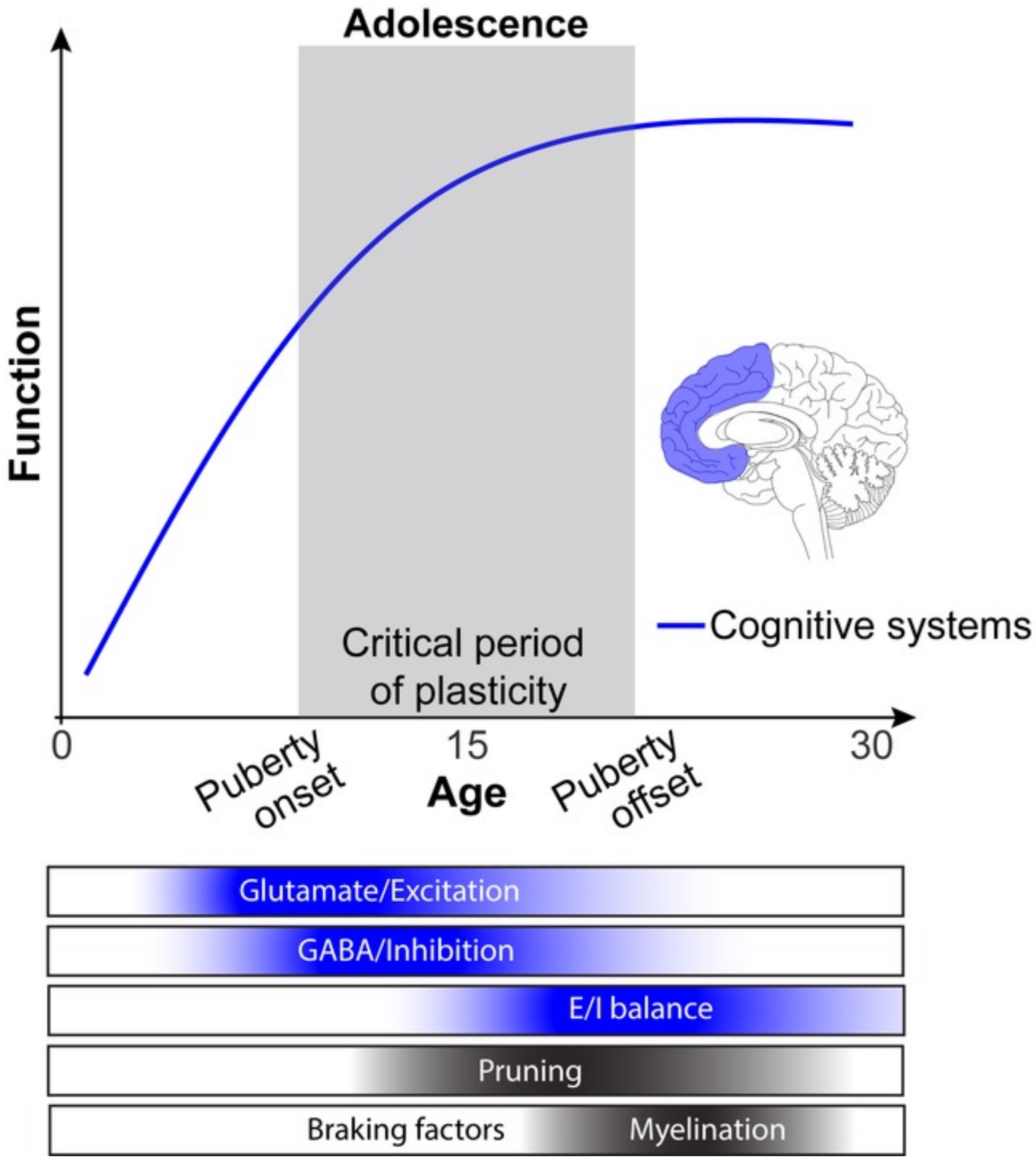
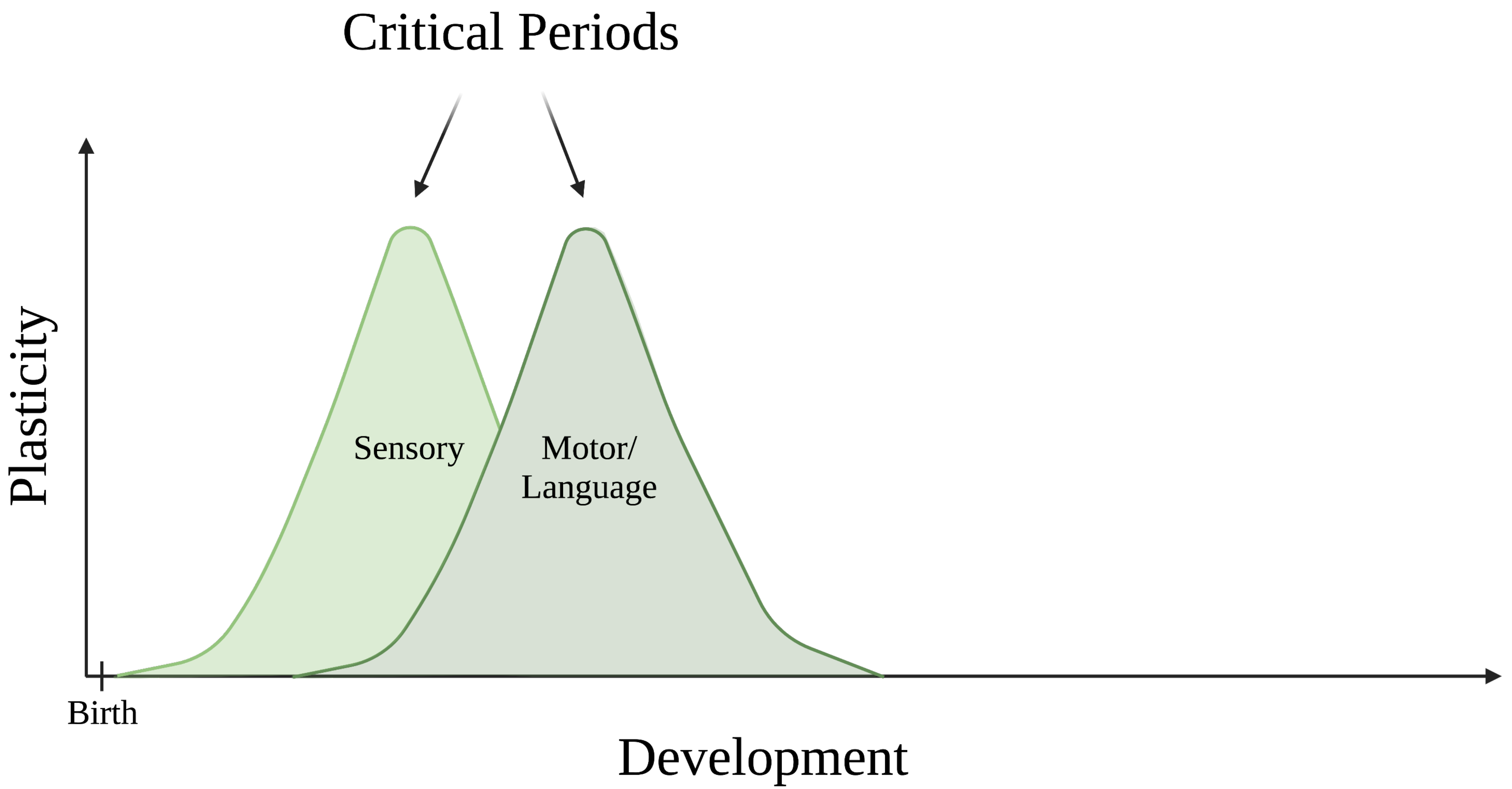


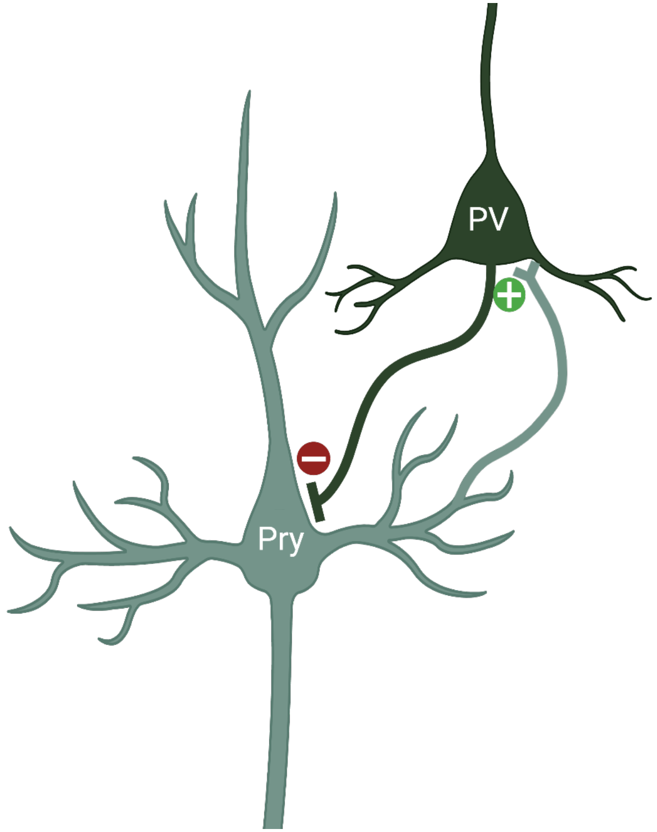


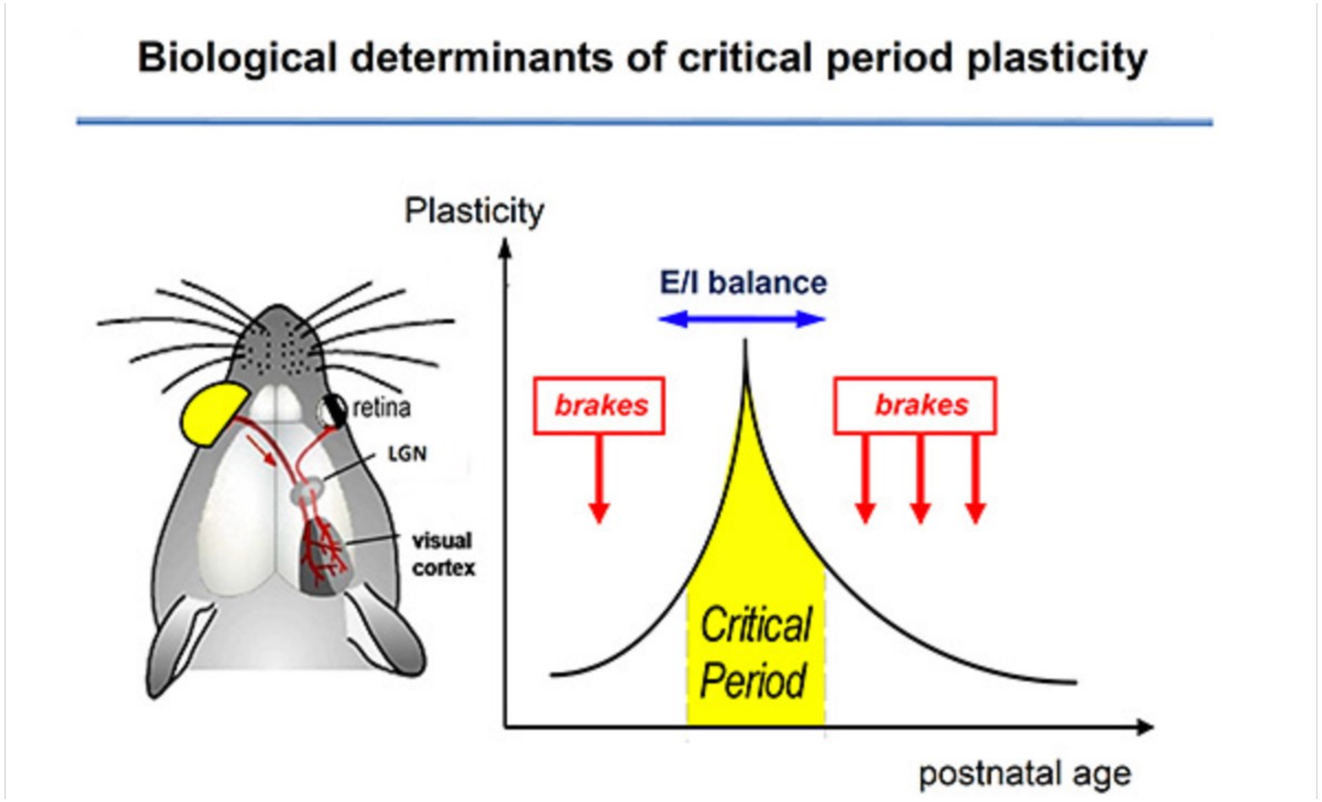
Ravindranath, Parr et al., 2022; Luna & Wright, 2015



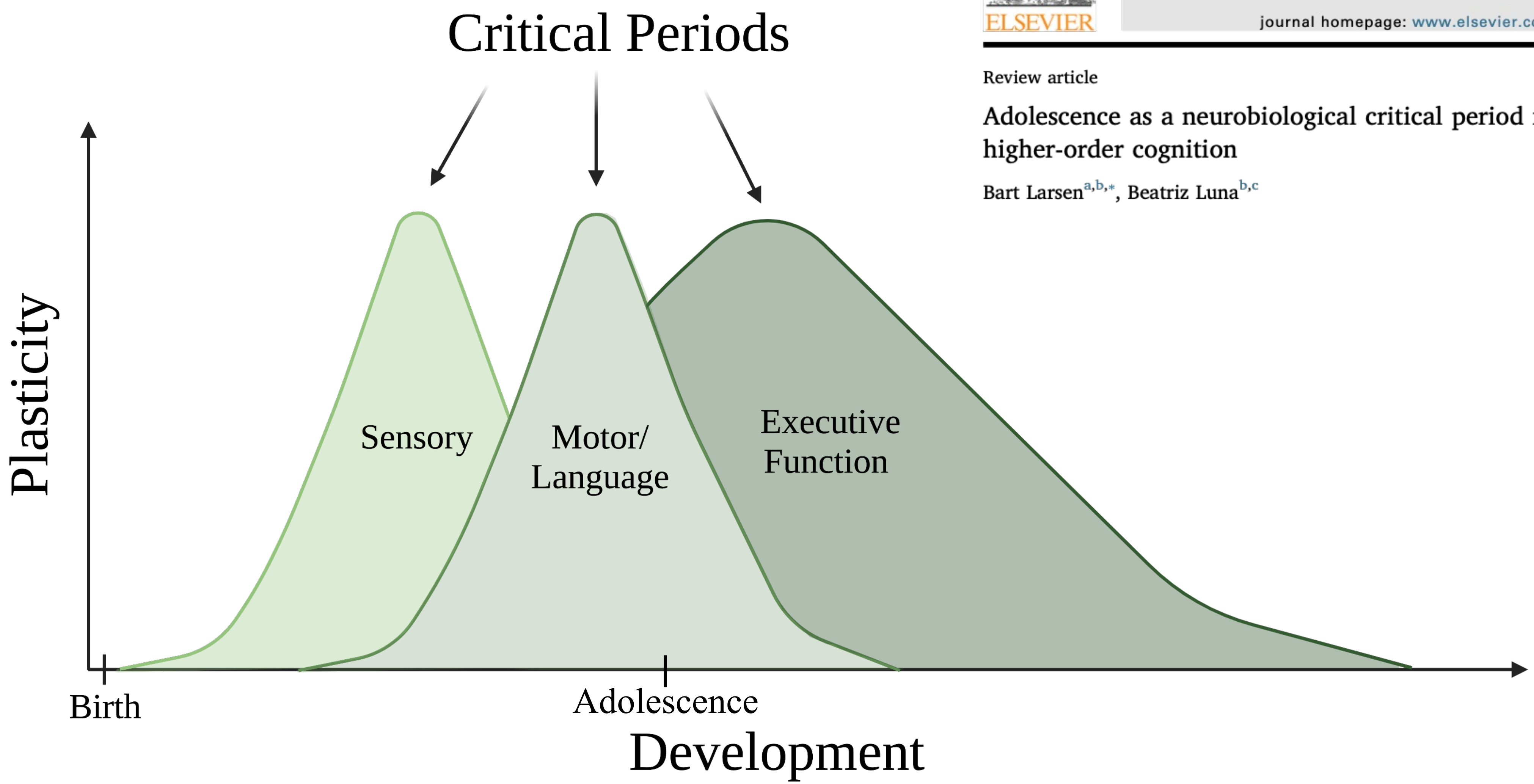
Critical Periods
Plasticity
Sensory
Motor/
Language
Birth
Development

Increase in excitatory activity shifts balance toward excitation → Maturation of inhibitory activity shifts balance toward inhibition → Closing factors stabilize circuitry





Adapted from Takao Hensch
https://ircn.jp/en/mission/people/takao_k_hensch



Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Adolescence as a neurobiological critical period for the development of higher-order cognition

Bart Larsen[a,b,*], Beatriz Luna[b,c]

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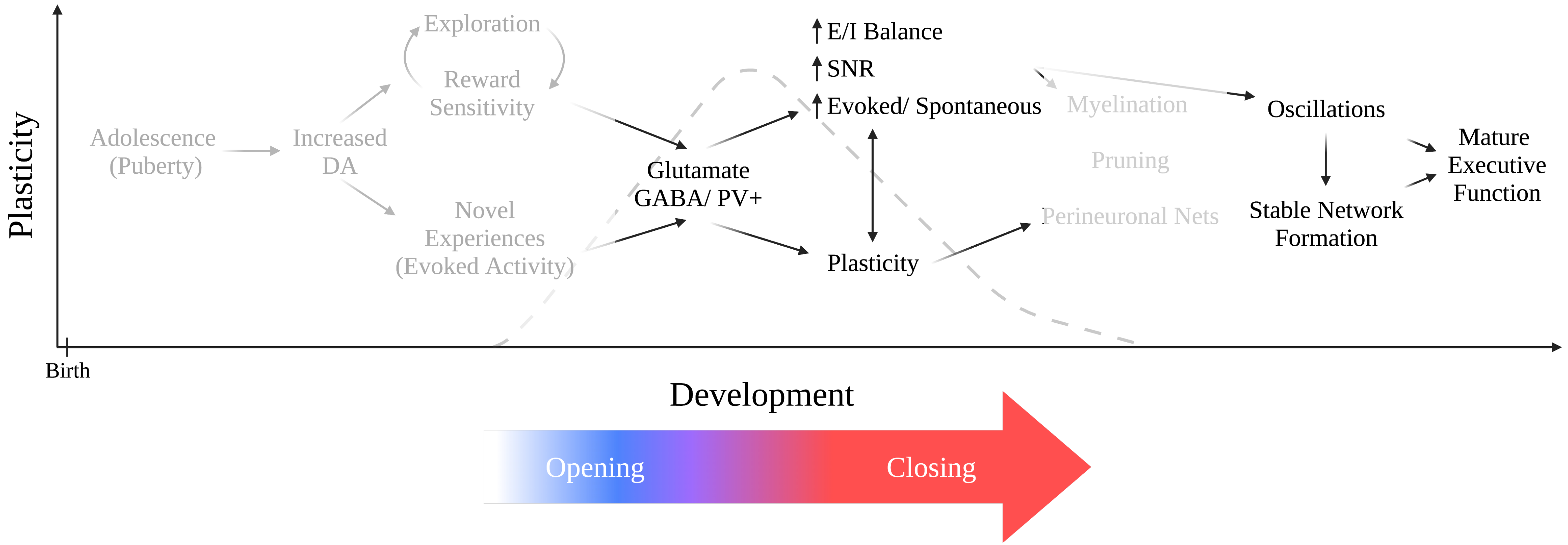
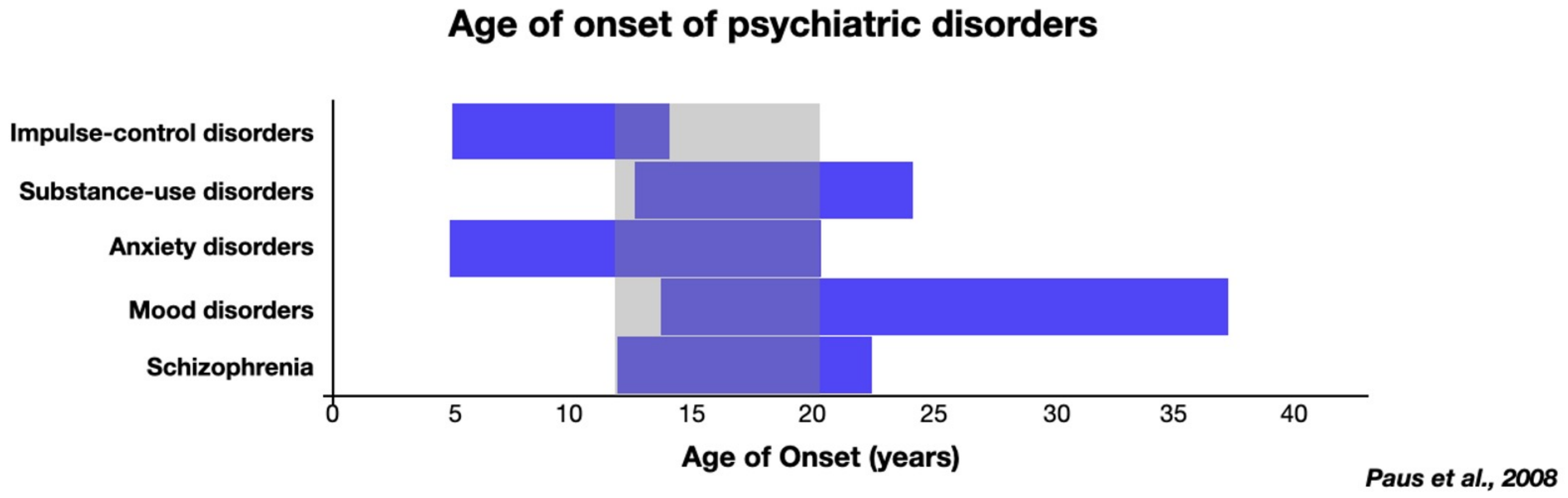
Review article

Adolescence as a neurobiological critical period for the development of higher-order cognition

Bart Larsen[a,b,*], Beatriz Luna[b,c]

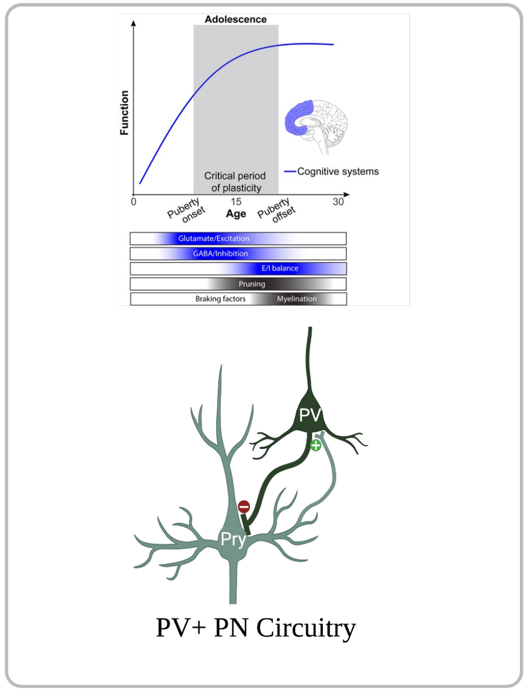


Adapted from Larsen & Luna, 2018

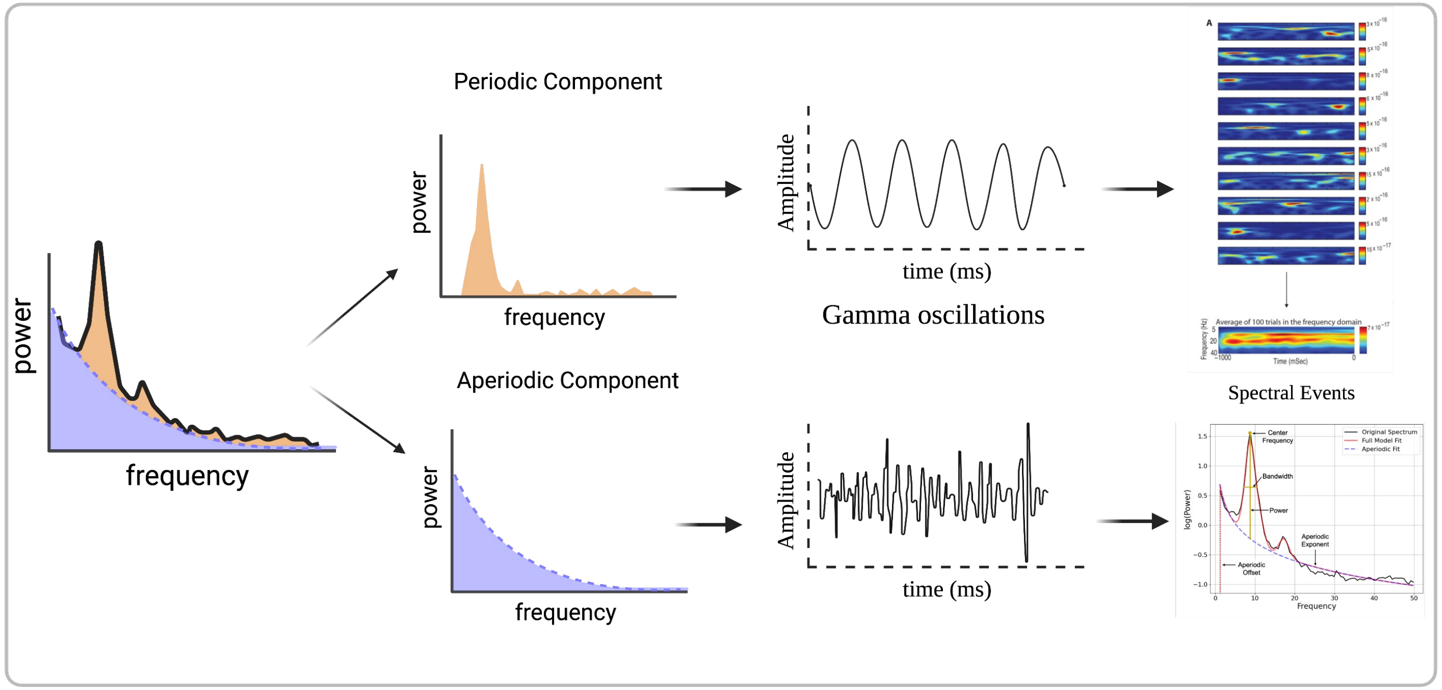

Age of onset of psychiatric disorders
Impulse-control disorders
Substance-use disorders
Anxiety disorders
Mood disorders
Schizophrenia
0
5
10
15
20
25
30
35
40
Age of Onset (years)
Paus et al., 2008

Will leverage a large, multimodal longitudinal dataset that will assess critical period plasticity during adolescence via the neural underpinnings of working memory and the developmental changes of the E/I balance

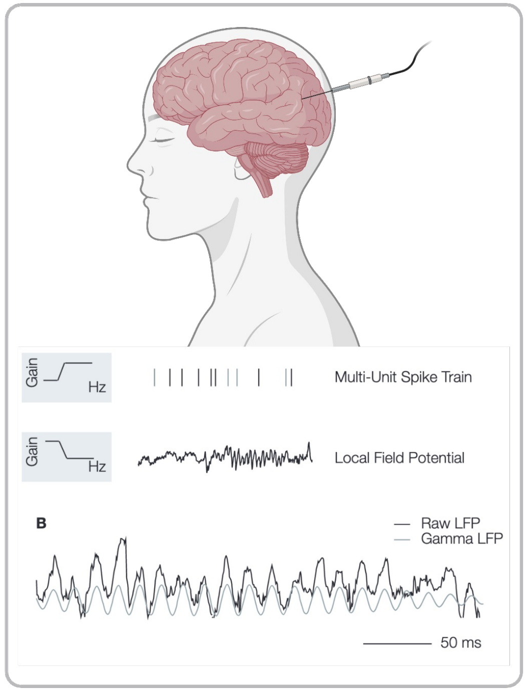
Introduction



Aim 1 & 2



Aim 3



Aim 1

Investigate associations in DLPFC between developmental changes in **EEG oscillations during WM and MRSI evidence of E/I**

Aim 2

Investigate associations in DLPFC between developmental changes in **aperiodic EEG measures of E/I and MRSI evidence of E/I**

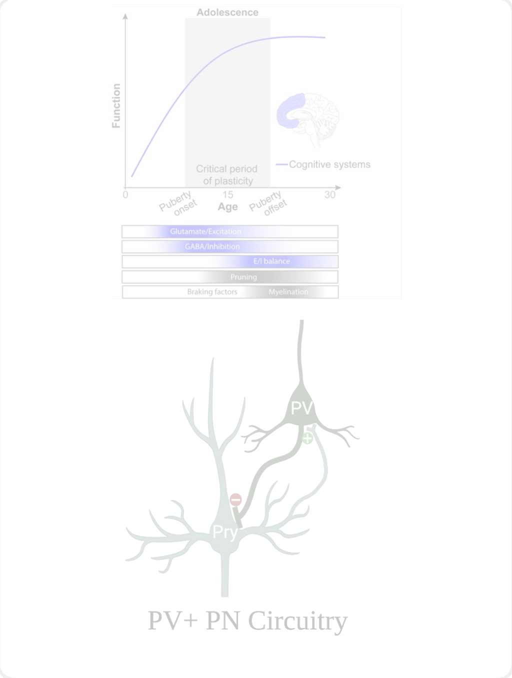
Aim 3

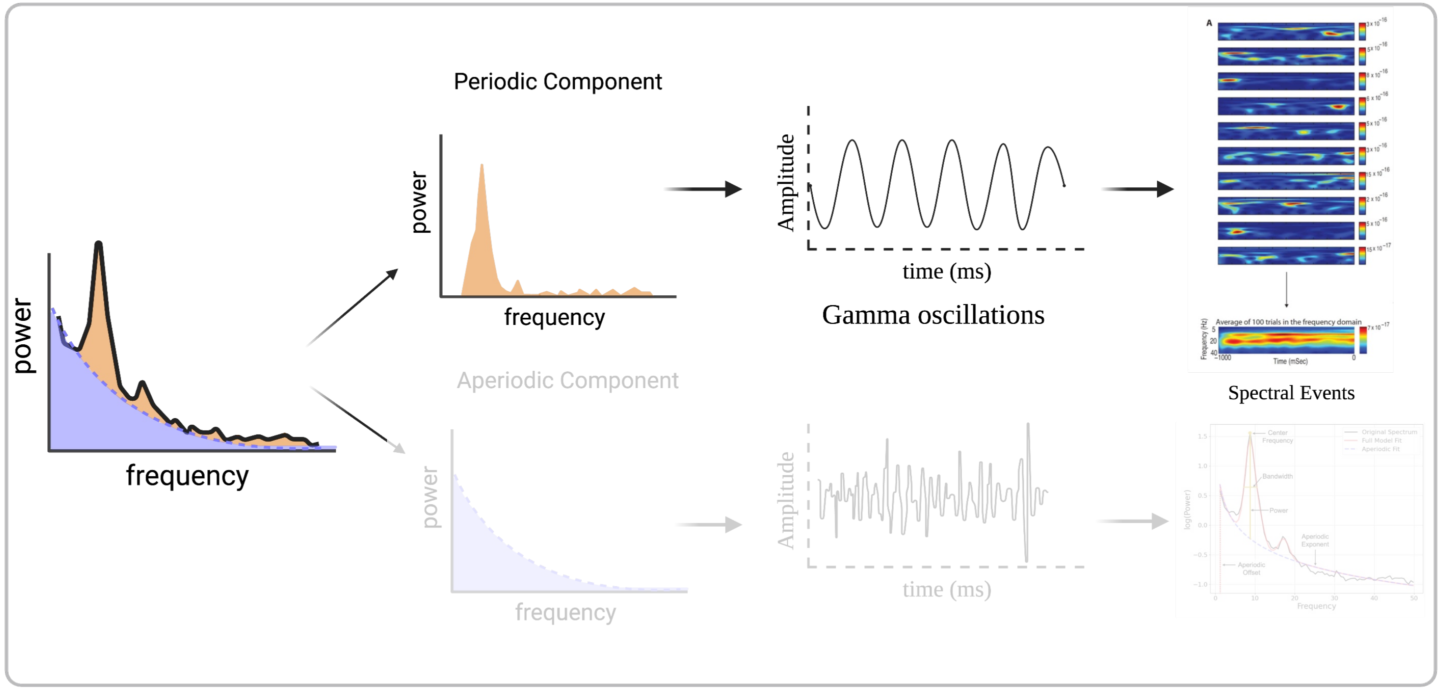
Characterize **properties of neural activity** underlying developmental changes in EEG measures of E/I using **sEEG**

Introduction

Aim 1

Aim 3





Investigate the neuronal underpinnings that support working memory improvement across adolescence during heightened plasticity

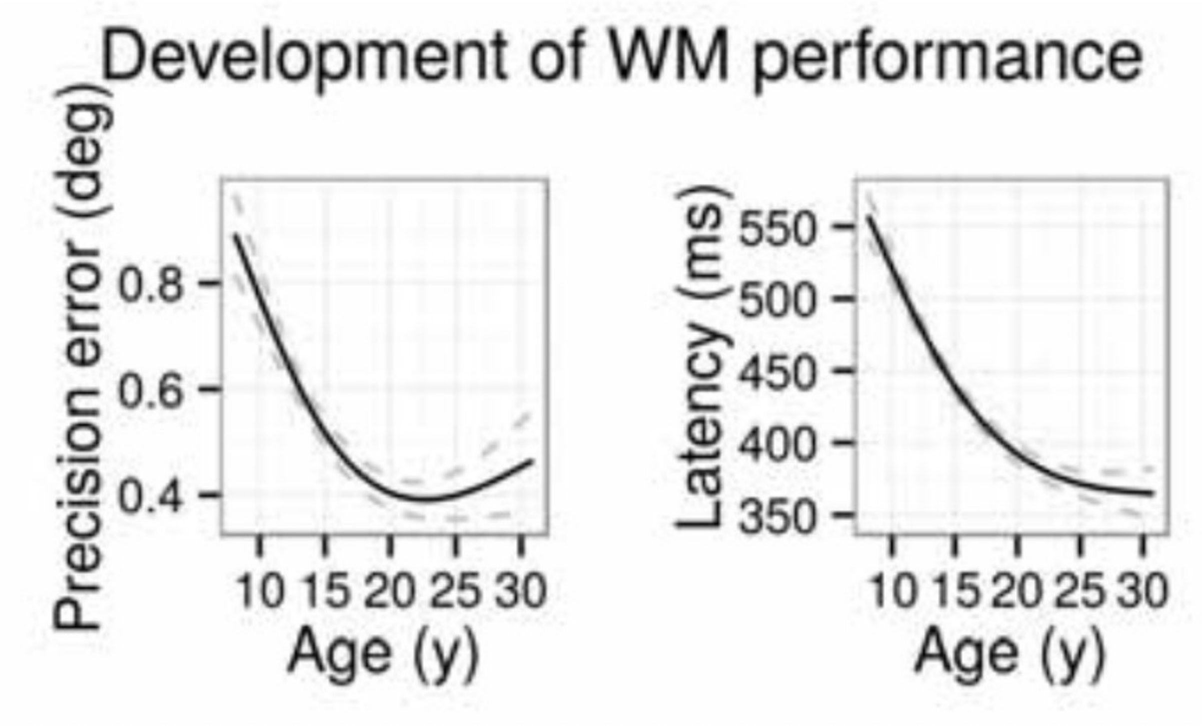
Aim 1

Investigate associations in DLPFC between developmental changes in **EEG oscillations during WM and MRSI evidence of E/I**

H1.1 Gamma band power will decrease with age in conjunction with a stabilization of cognitive function into adulthood, as seen in performance improvement in the WM task

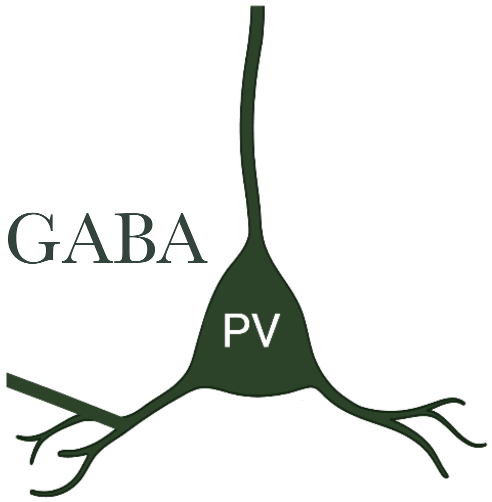
H1.2 Developmental changes in Glu and GABA will mediate age-related changes in EEG activity, providing a mechanistic framework for development improvements in WM.

Continued improvement in executive function, including working memory, seen in improved accuracy and a reduction in response latency



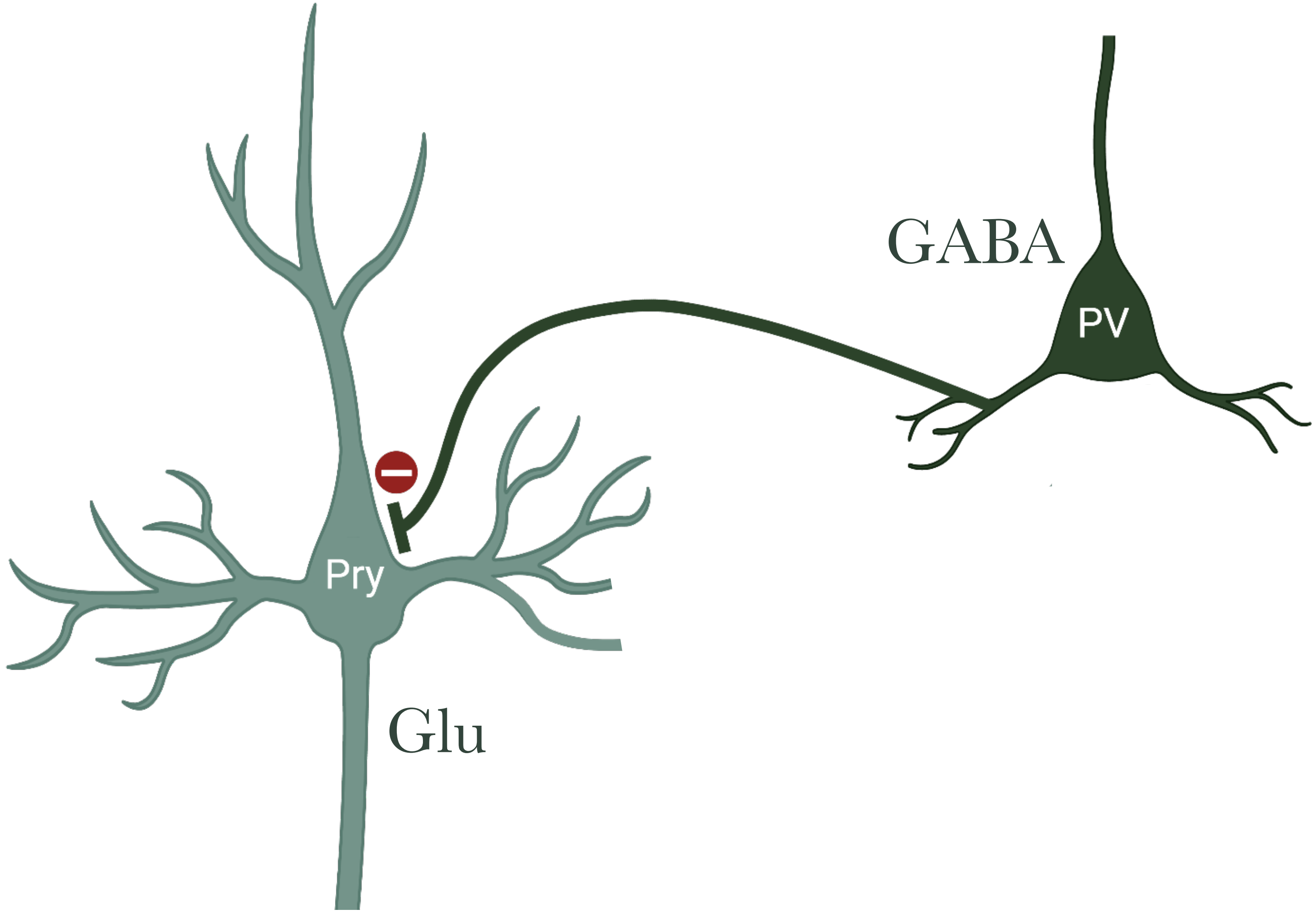
Simmonds et al, 2017

Maturation of PFC parvalbumin (PV) positive basket cells support executive function[1]



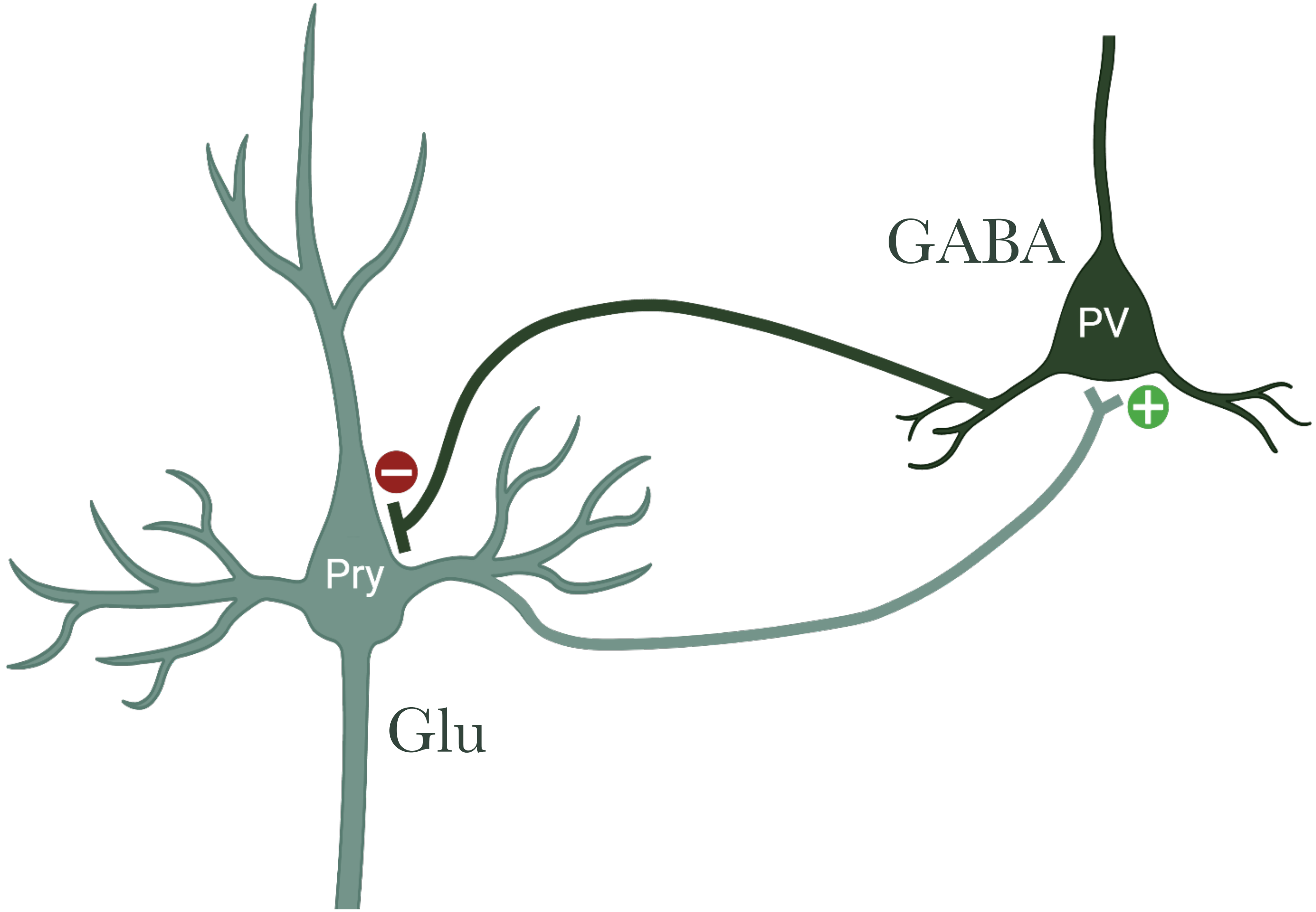
1. Ferguson & Gao (2018). 2. Toyoizymi (2013). 3. Katz (1996). 4. Bosman (2002). 5. Katagiri (2007)

Maturation of PFC parvalbumin (PV) positive basket cells support executive function[1]



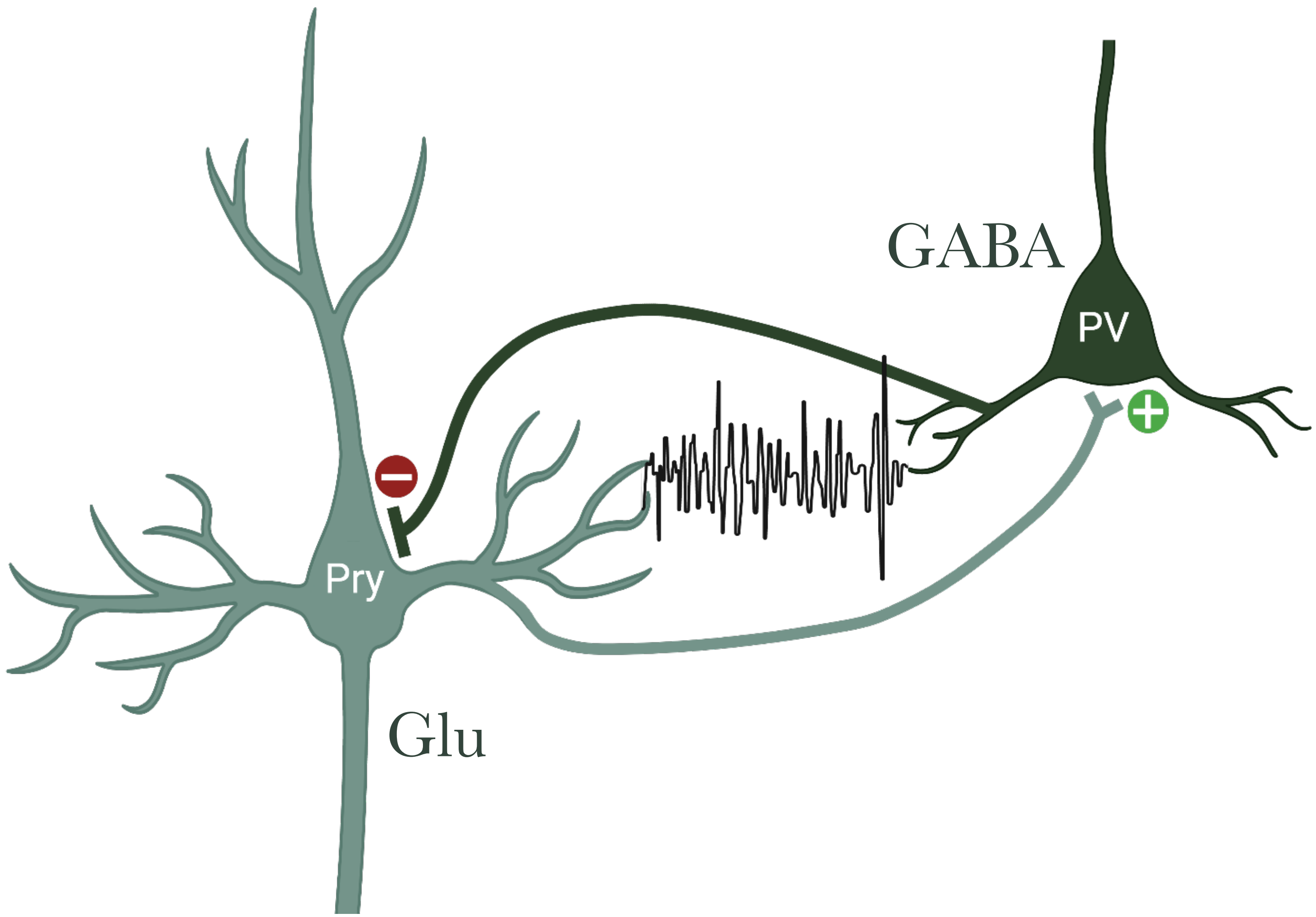
1. Ferguson & Gao (2018).

Synchronize pyramidal cell population activity within and between cortical networks[1]

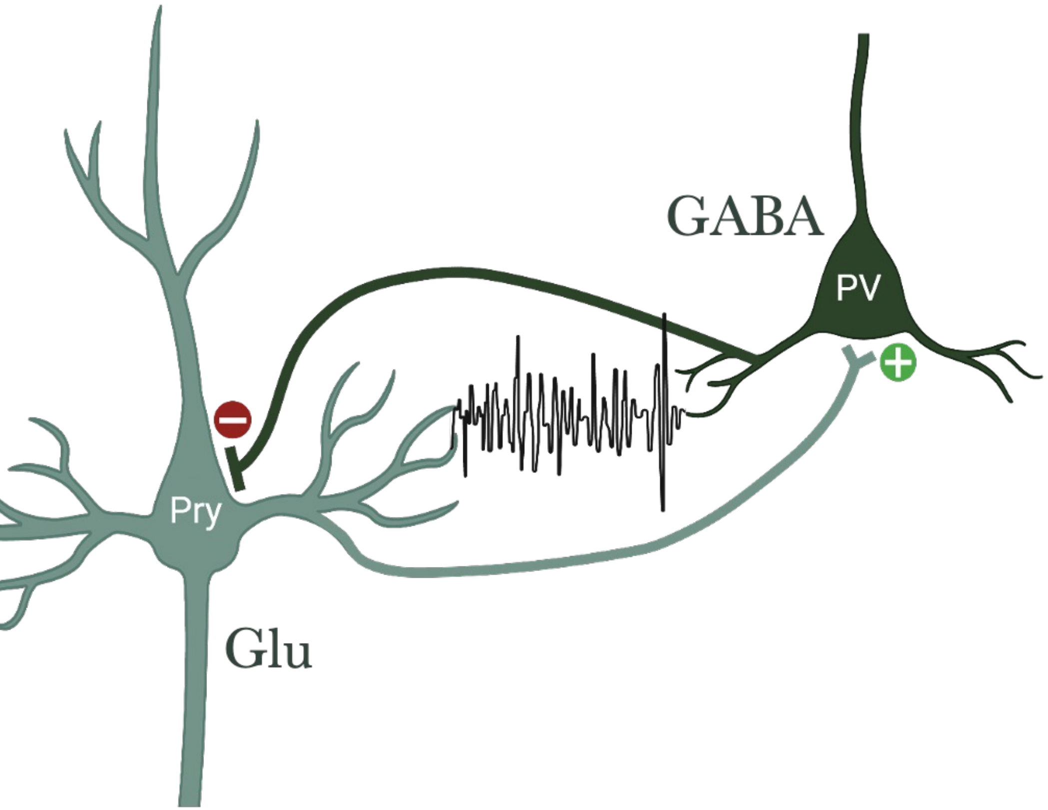


1. Ferguson & Gao (2018).

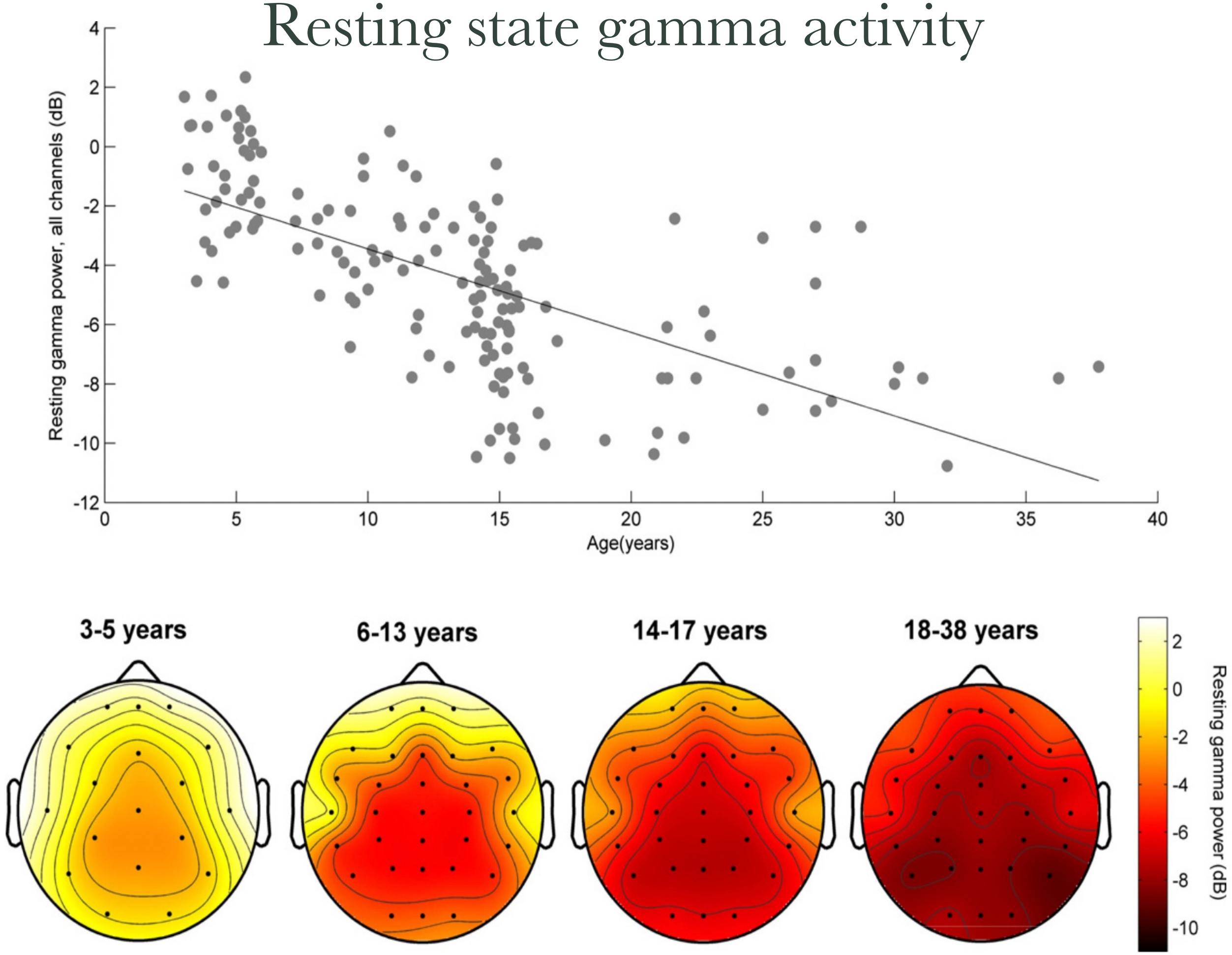
Producing gamma oscillations, and suppressing spontaneous neural activity



Age-related decreases in gamma power may be indicative of structural changes such as decreases in synaptic pruning



Resting state gamma activity

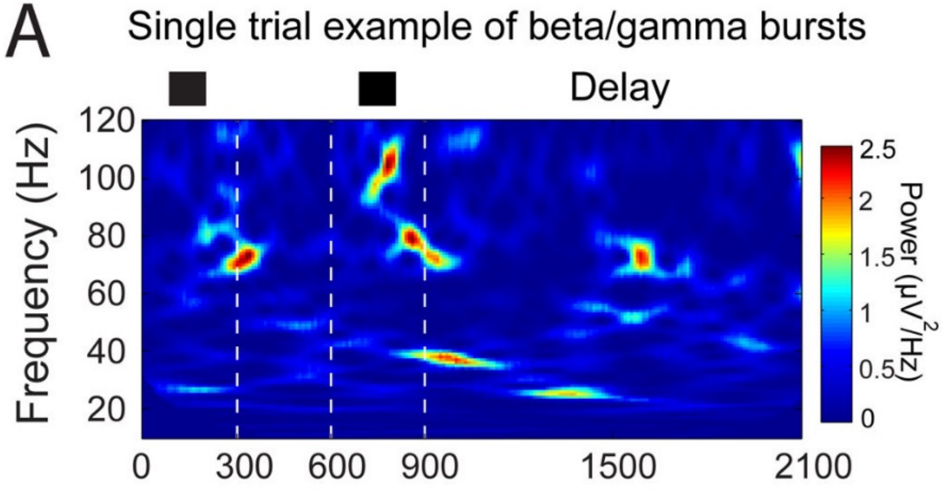


Tierney, et al. 2013

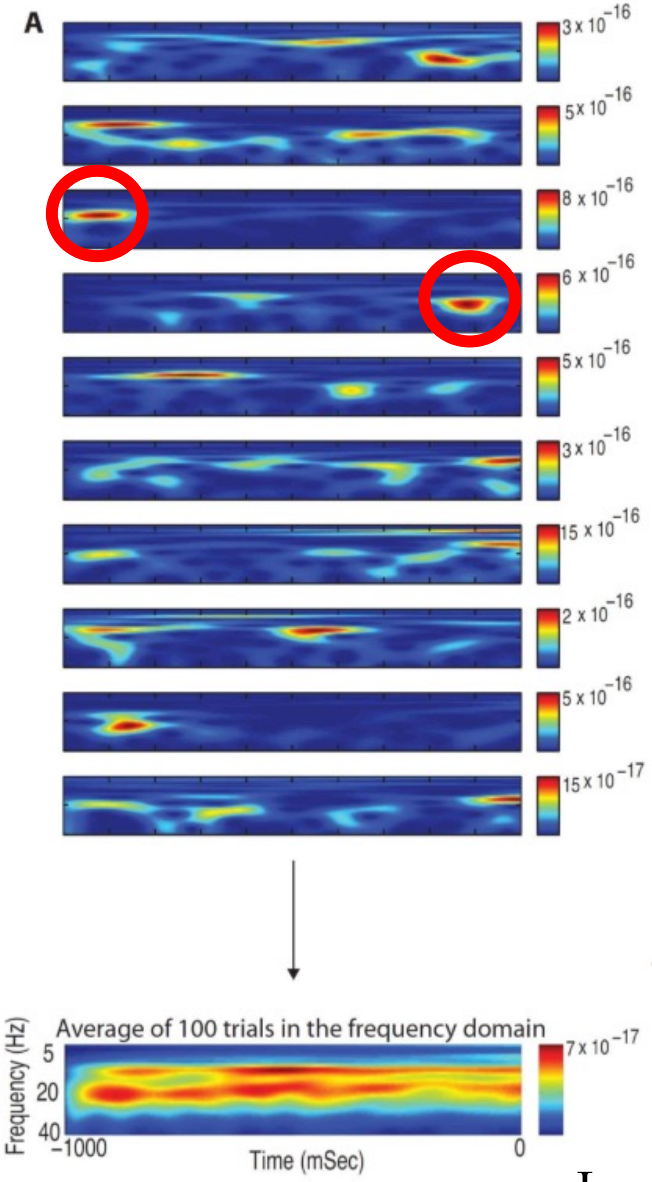
Trial level neural activity occurs in burst like events[1]

Timing, duration, and rate of the events play a key role in supporting higher order cognitive functions, such as working memory[1]

Working memory has since been shown to be non-stationary, with information stored as temporary changes in synaptic weights[2-9]



Miller, 2018



Jones, 2016

Aim 1: Background

1. Jones, S. R (2016). 2. Lundqvist (2018). 3. Goldman-Rakic (1995). 4. Miller (1996). 5. Quinn (2019). 6. Shin (2017). 7. Lundqvist (2016). 8. Hirschmann (2020). 9. Lunqqvist (2018).

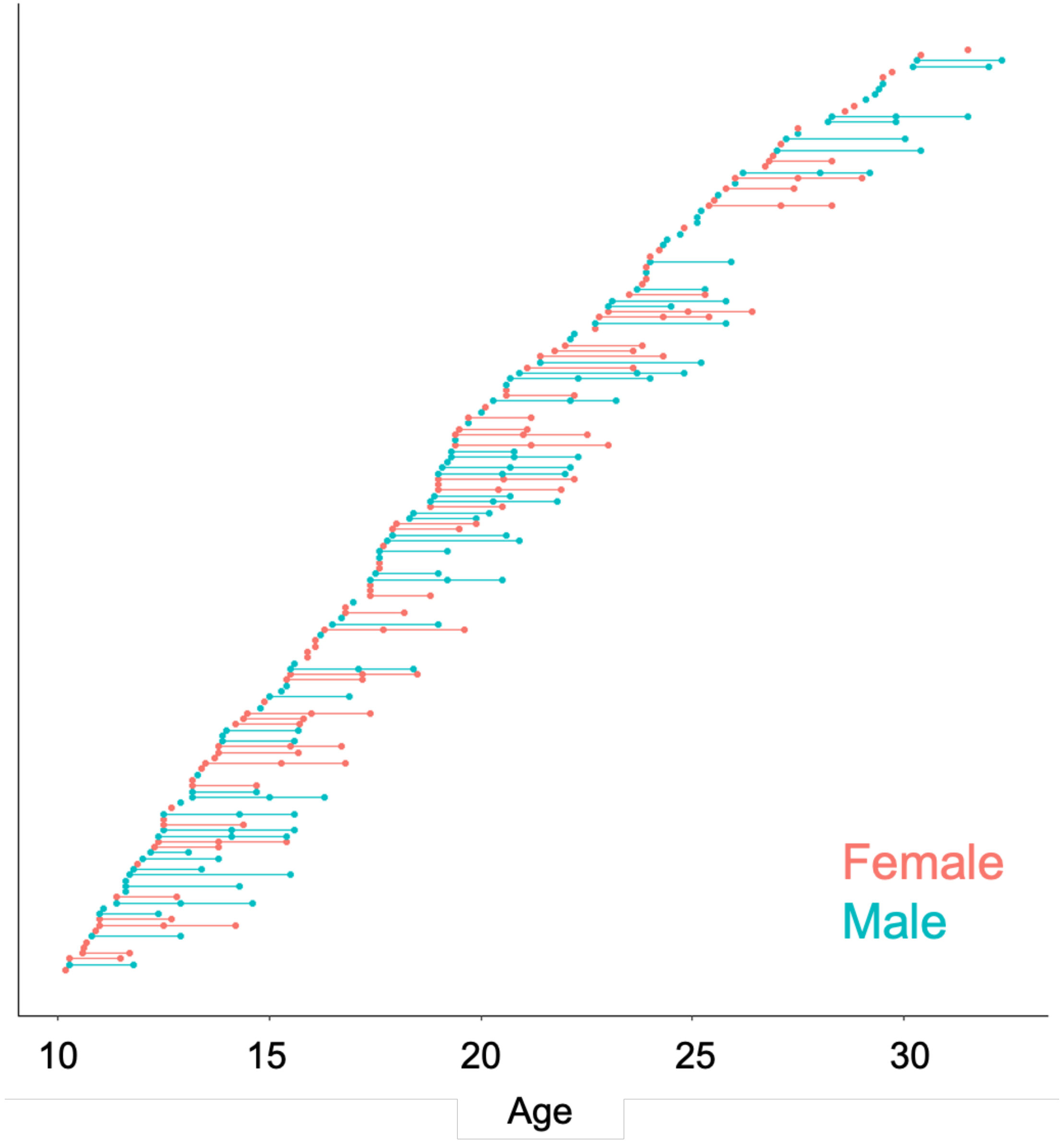
We will assess the relationship between spectral bursts of activity in the gamma band and working memory

164 participants (87 female at birth)

Up to 3 visits per person (a behavioral (in-lab) session, a 7T MRI scan, and an EEG session) at 18-month intervals for a total of 286 scans

Exclusion Criteria:

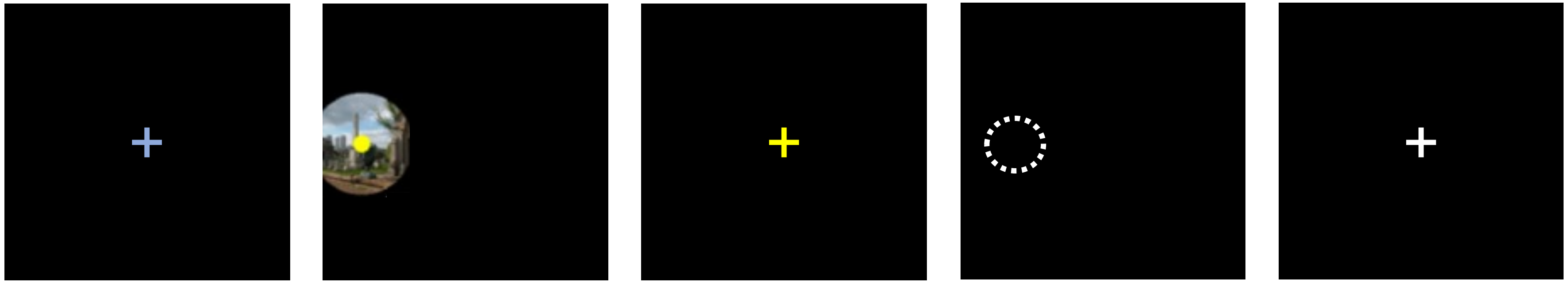
- A history of head injury
- A history of substance abuse
- History of major psychiatric or neurological conditions in themselves or a first-degree relative
- MRI contradictions (metal, claustrophobic)



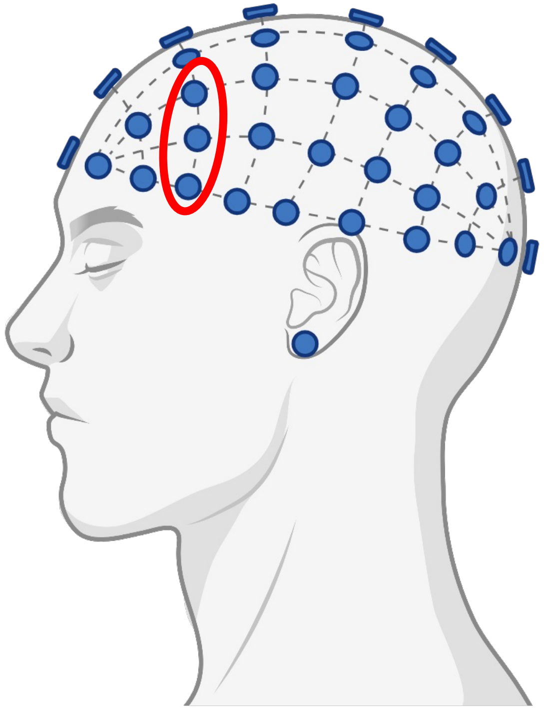
Aim 1: Methods

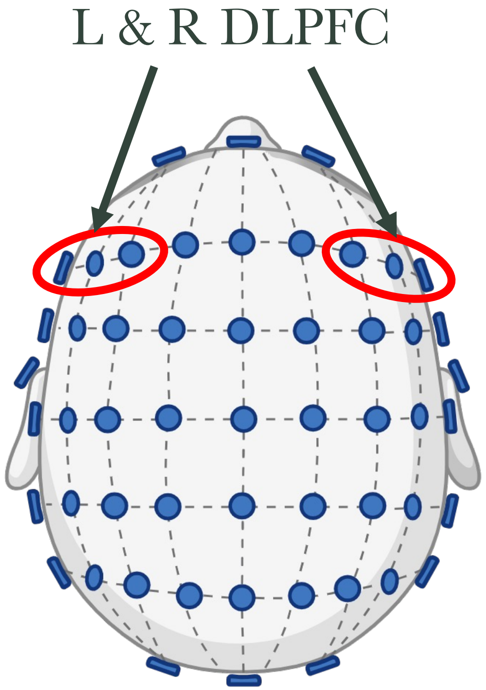
Participants performed a memory guided saccade (MGS) task to assess working memory.

Fixation	VGS	Delay	MGS	ITI
1 sec.	1 sec.	6-10 sec.	1 sec	1.5 – 15 sec

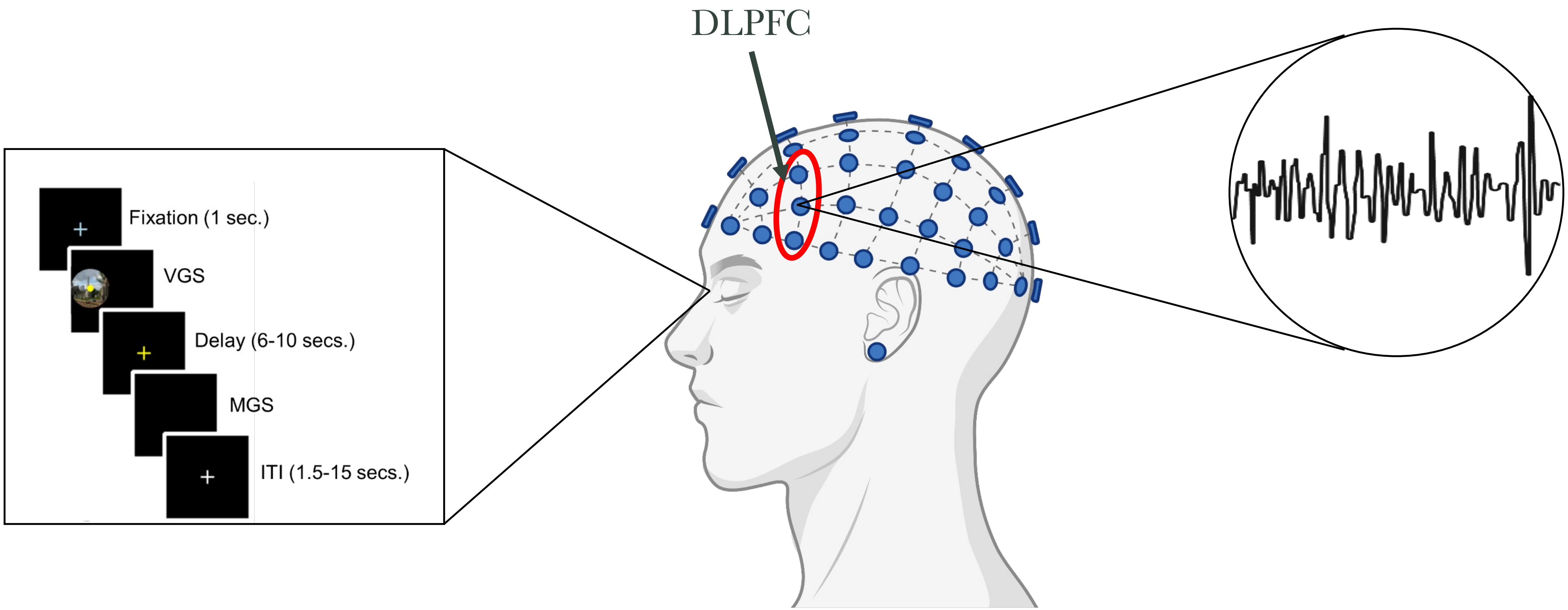


	Encoding	Retention	Retrieval	

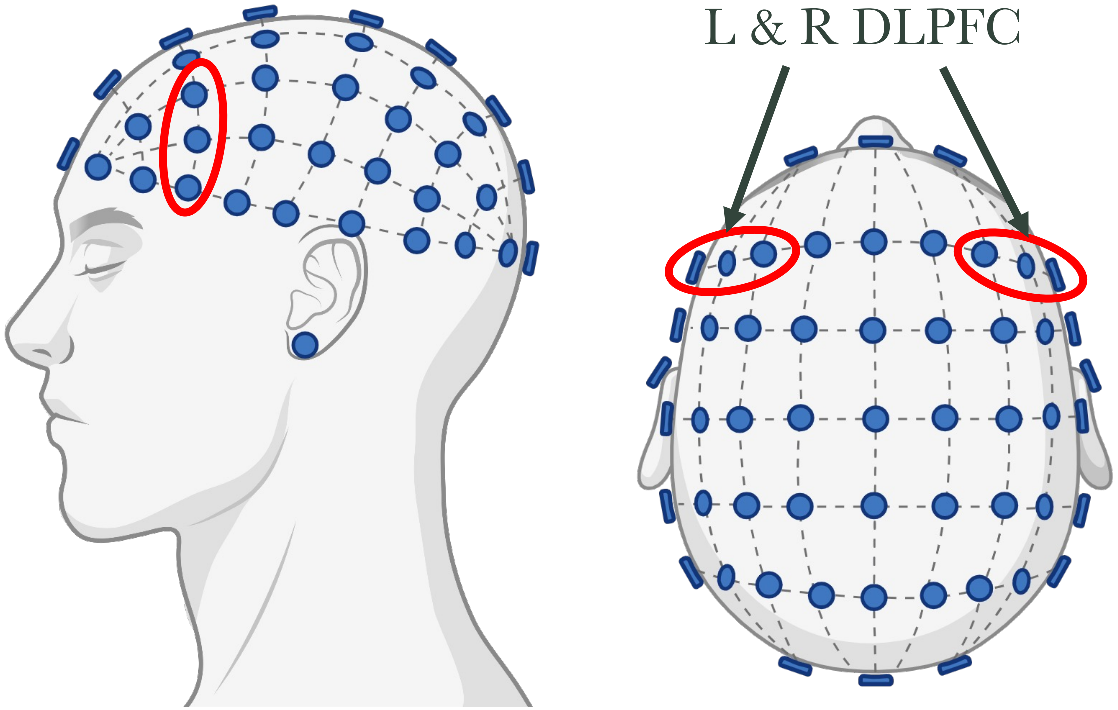




Concurrent EOG (electrooculogram) and high-impedance EEG was recorded using a Biosemi ActiveTwo 64-channel EEG system

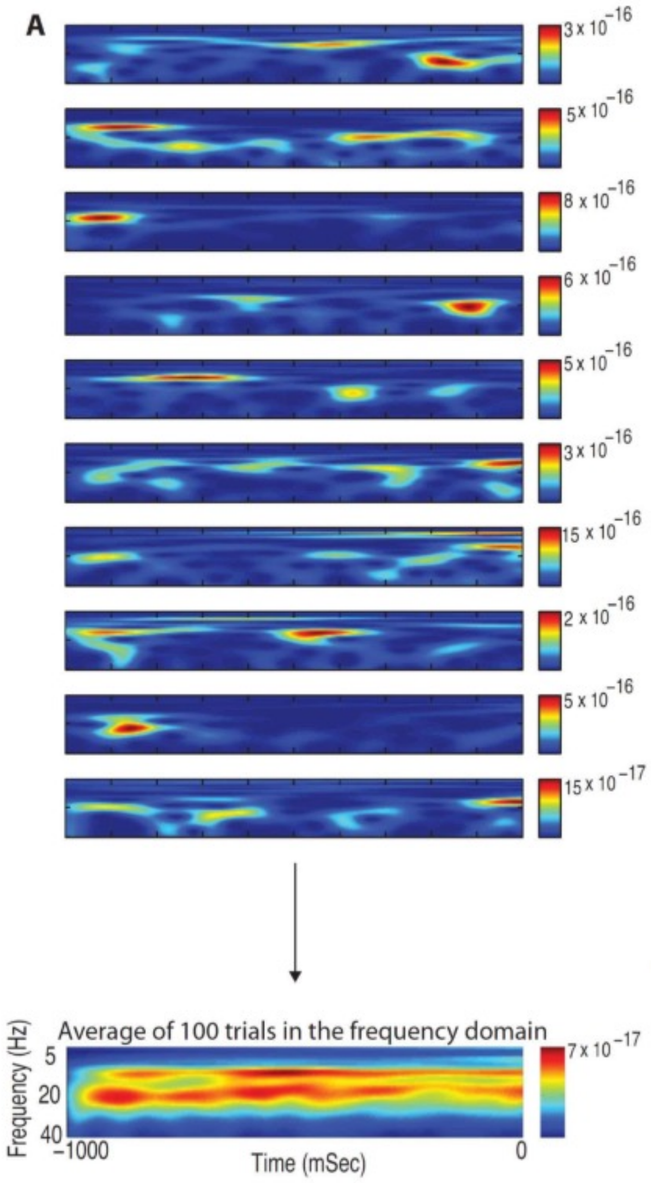


Aim 1: Background



Preprocessing

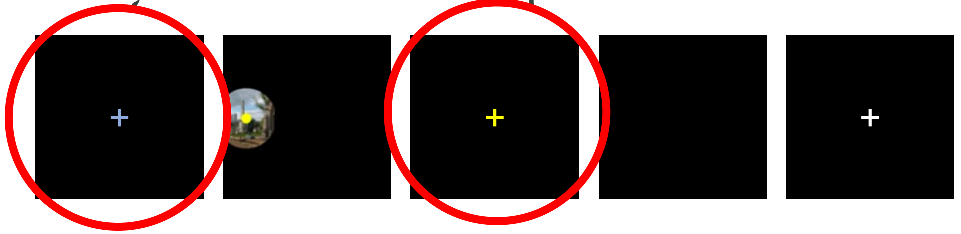
- Downsampled to 150hz
- Referenced to the mastoids
- Bandpassed between 0.5 – 75 Hz
- ICA to remove eye movement/ blink artifact



Jones, 2016

Spectral Event Analysis

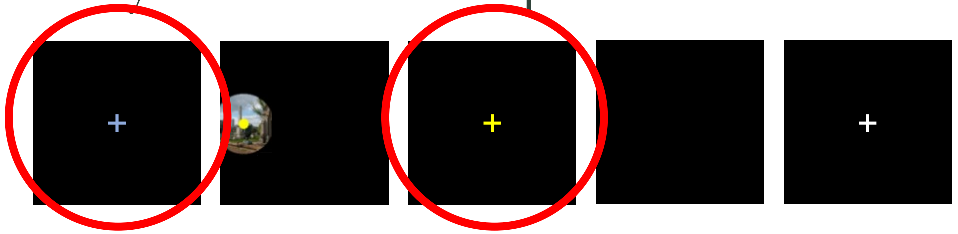
- Spectral data is computed from 1 second data windows
  - Delay and fixation epochs



- Time frequency response will be calculated using the Morlet wavelet

Spectral Event Analysis

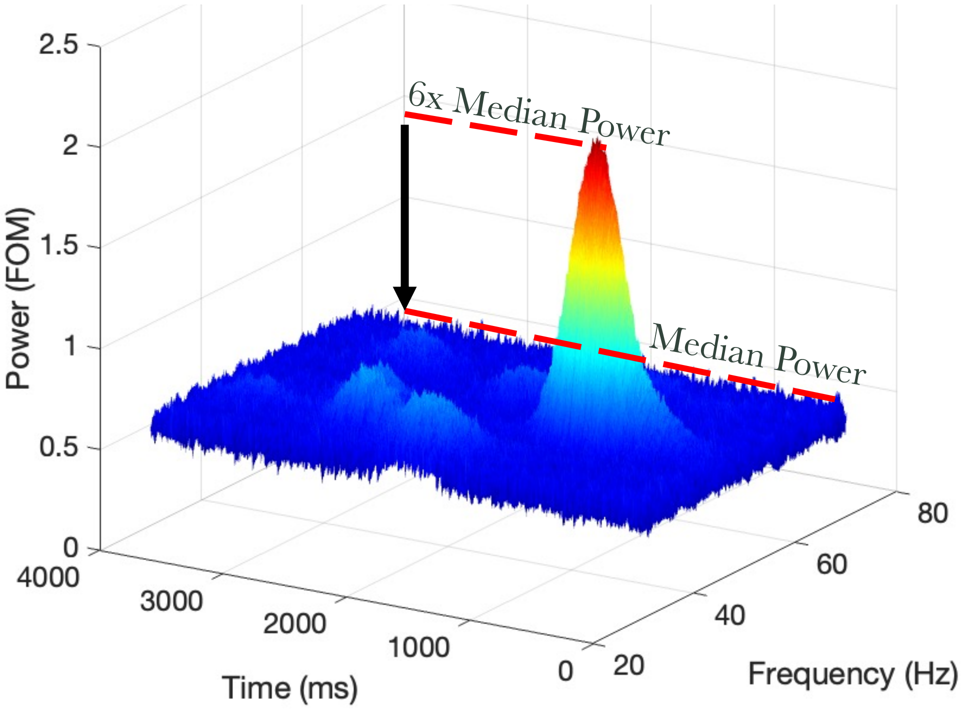
- Spectral data is computed from 1 second data windows
  - Delay and fixation epochs



Time frequency response will be calculated using the Morlet wavelet

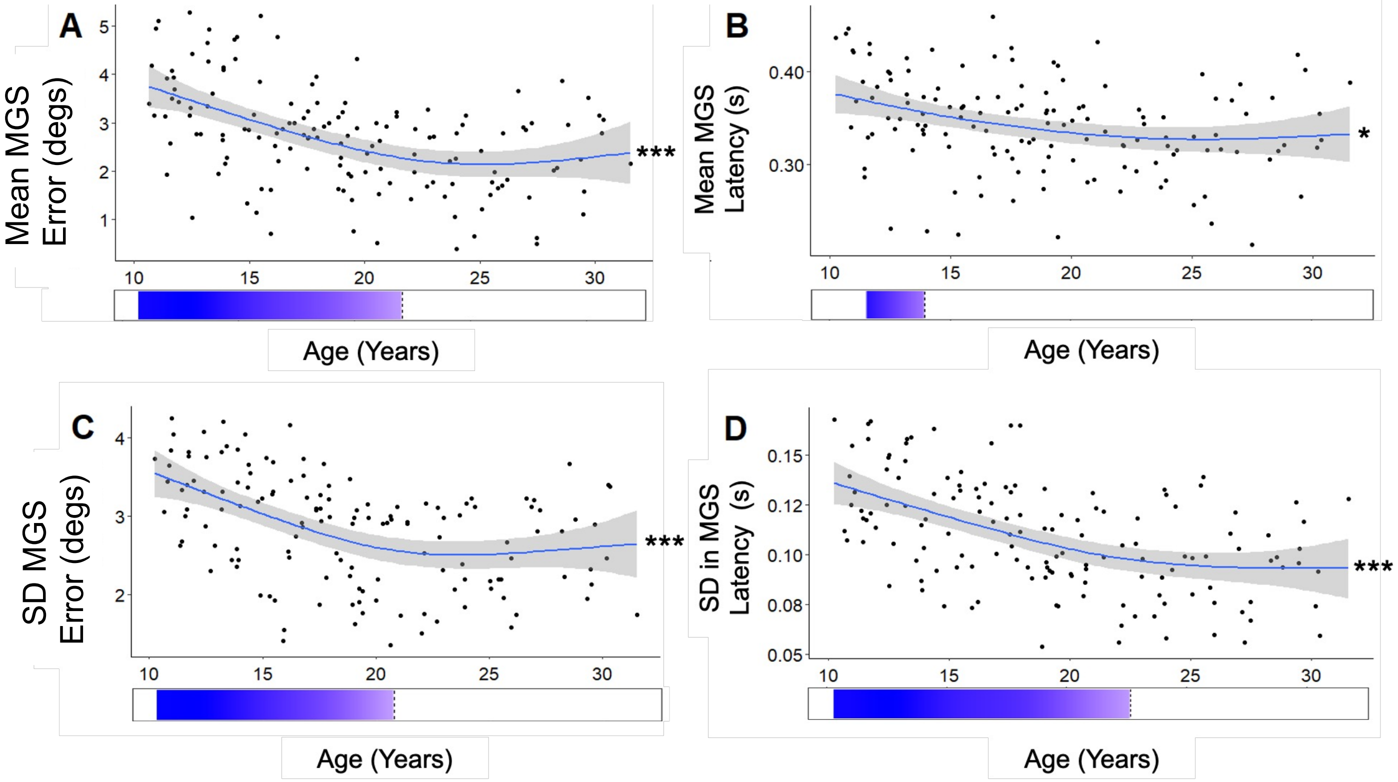
Spectral event measures for the gamma band (35-65 Hz)

- Power
- Number of events



Age-related differences in transient gamma band activity during working memory maintenance through adolescence

Shane D. McKeon [1 2], Finnegan Calabro [1 2 3], Ryan V. Thorpe [4], Alethia de la Fuente [5 6 7], Will Foran [3], Ashley C. Parr [2 3], Stephanie R. Jones [4], Beatriz Luna [2 3]

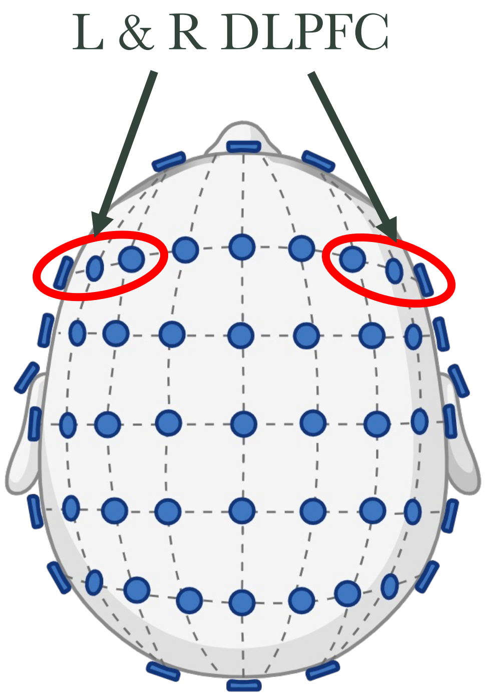


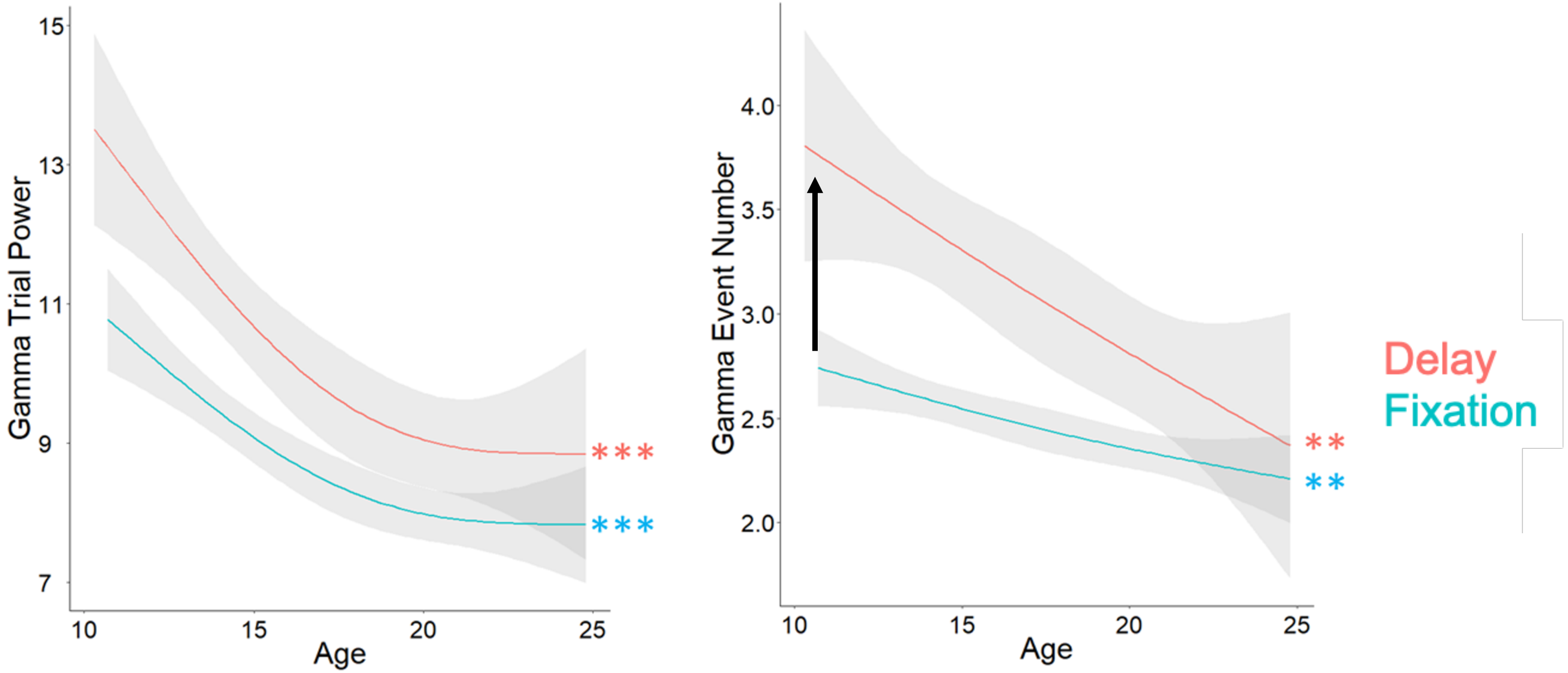
Consistent with previous literature[1,2], working memory performance improved into adulthood including increased accuracy and decreased response latency to make a goal-directed response.

1. Luna (2015). 2. Larsen (2018)

Age-related differences in transient gamma band activity during working memory maintenance through adolescence

Shane D. McKeon [1 2], Finnegan Calabro [1 2 3], Ryan V. Thorpe [4], Alethia de la Fuente [5 6 7], Will Foran [3], Ashley C. Parr [2 3], Stephanie R. Jones [4], Beatriz Luna [2 3]





01

Spectral activity properties (power, duration, and number of events) vs age and behavioral performance in our longitudinal data set (H1.1).

Gamma power ↓ as accuracy ↑ and response latency ↓

02

Mediation analyses to test whether age-related changes in EEG activity are explained by age-related changes in Glu/GABA balance (H1.2).

Aim 1: Next Steps & Expected Outcomes

Investigate the neuronal underpinnings that support working memory improvement across adolescence during heightened plasticity

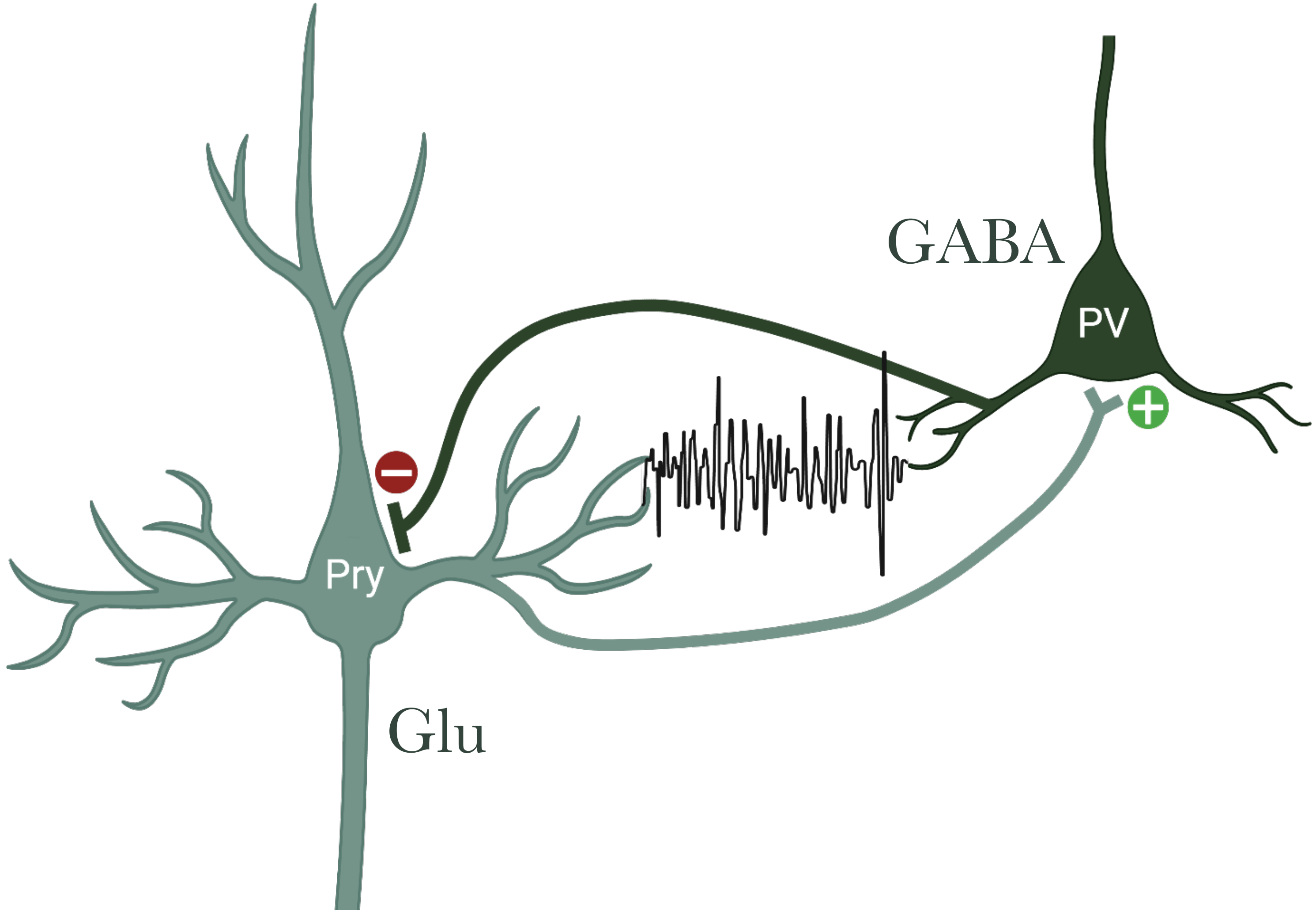
Aim 1

Investigate associations in DLPFC between developmental changes in **EEG oscillations during WM and MRSI evidence of E/I**

H1.1 Gamma band power will decrease with age in conjunction with a stabilization of cognitive function into adulthood, as seen in performance improvement in the WM task

H1.2 Developmental changes in Glu and GABA will mediate age-related changes in EEG activity, providing a mechanistic framework for development improvements in WM.

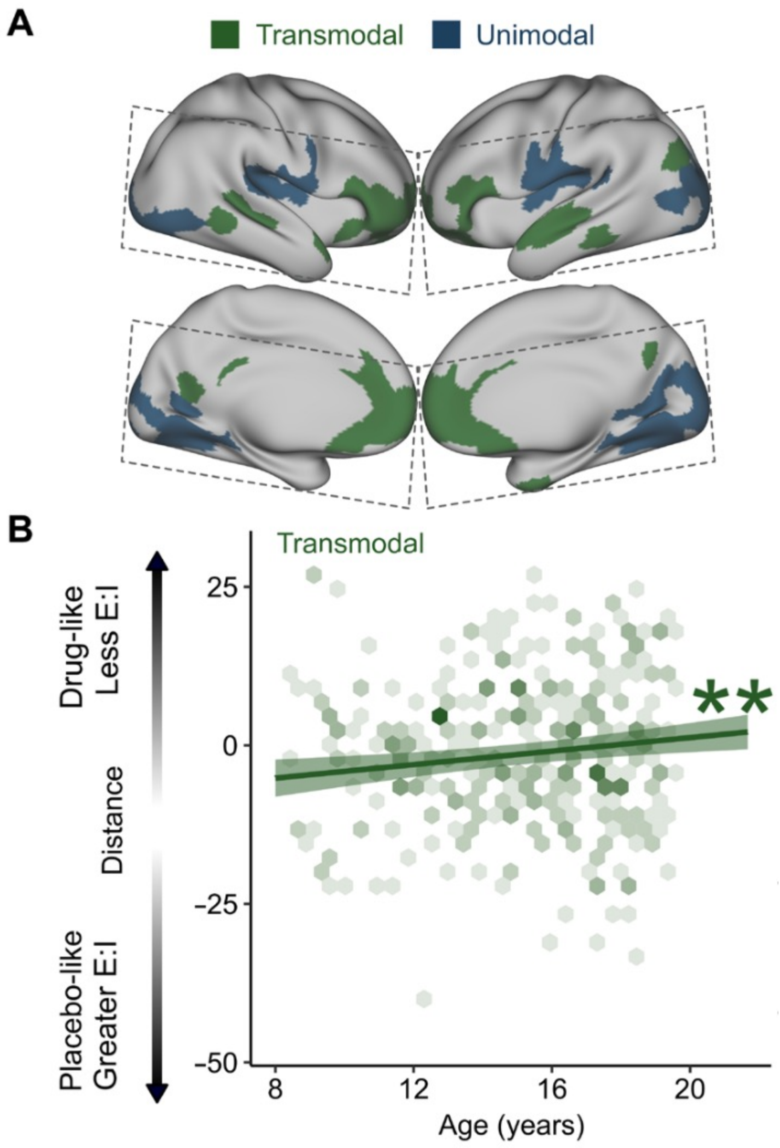
Support synaptic inhibition[1] and synaptic plasticity[2], both of which effectively increase E/I balance



1. Bosman (2002). 2. Katagiri (2007)

Benzodiazepine, effectively reducing the E/I ratio via increases in GABAergic inhibition.

Age-related (8-21.7 years) reductions of the E/I ratio were found within association cortices, consistent with characteristics of a critical period of adolescent development



Larsen, 2022

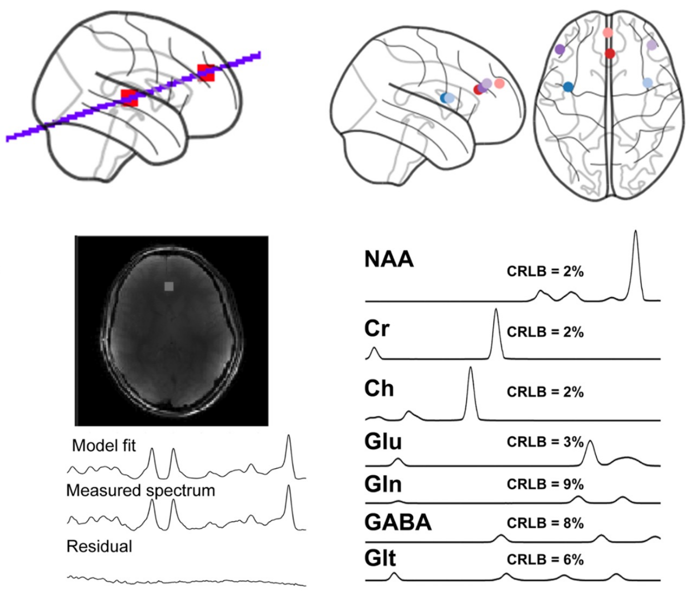
Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Development of frontal GABA and glutamate supports excitation/inhibition balance from adolescence into adulthood

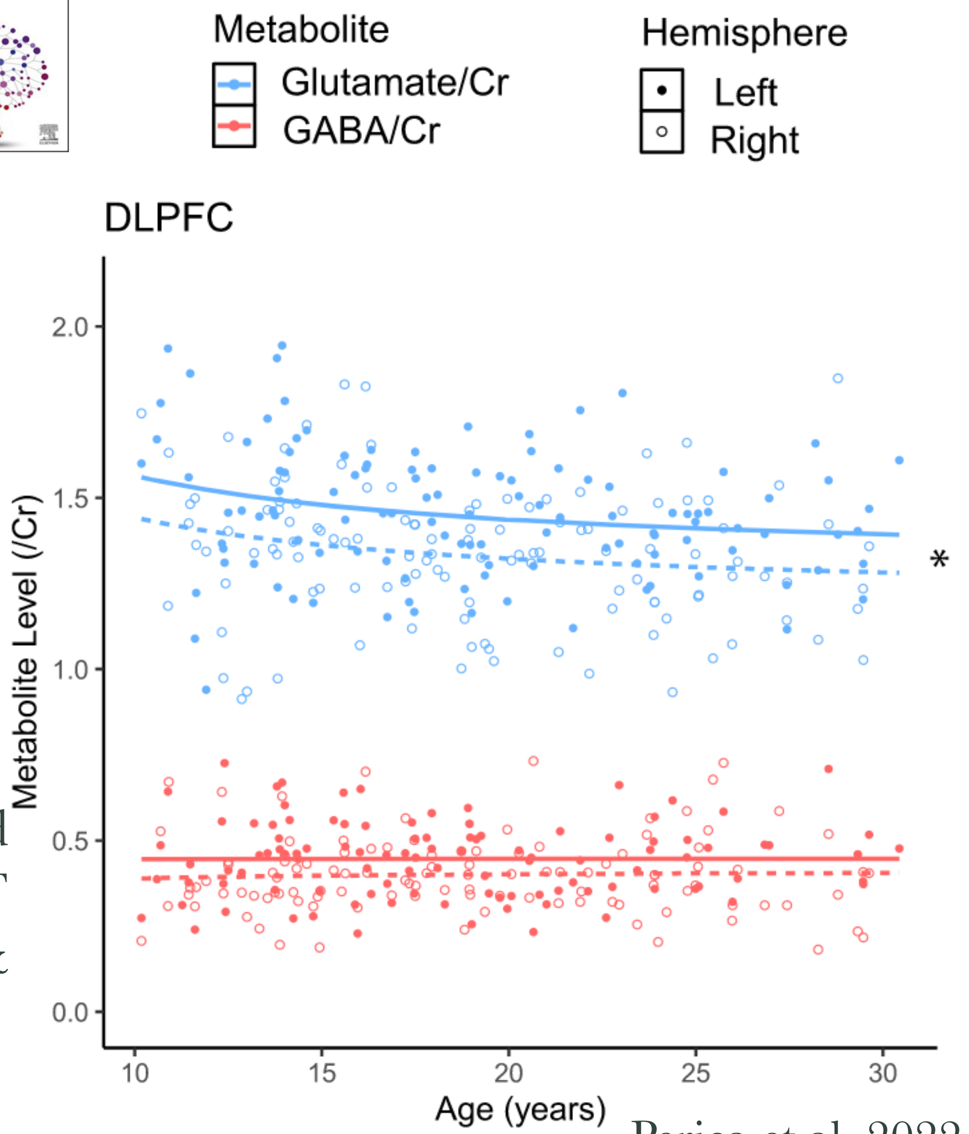
Maria I. Perica [a], Finnegan J. Calabro [b,c], Bart Larsen [d], Will Foran [b], Victor E. Yushmanov [e], Hoby Hetherington [f,g], Brenden Tervo-Clemmens [h], Chan-Hong Moon [e], Beatriz Luna [b,*]



Oblique slice of 24x24 voxels (1.0x0.9x0.9mm) using a J-refocused MRSI sequence (TE/TR = 35/1500ms)

Neurotransmitters (NT) quantified using LCModel and reflect the NT relative to creatine (Cr, Glu/CR & GABA/Cr)

*same subjects as EEG data set

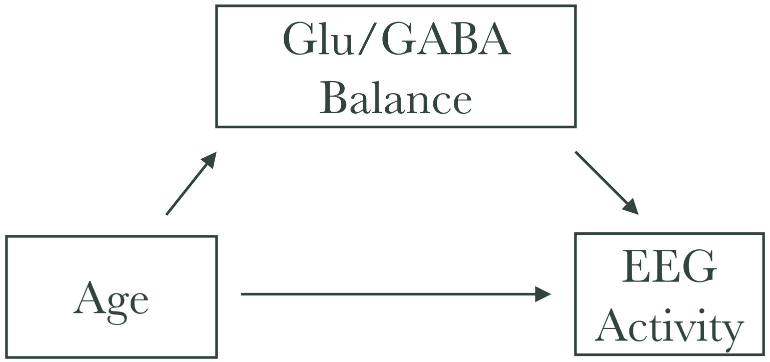


Perica et al, 2022

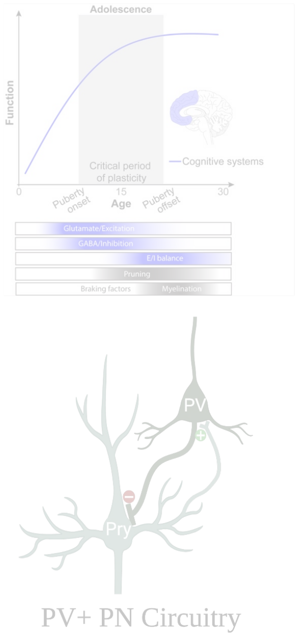
01 Spectral activity properties (power, duration, and number of events) vs age and behavioral performance in our longitudinal data set (H1.1).

Gamma power ↑ as accuracy ↑ and response latency ↓

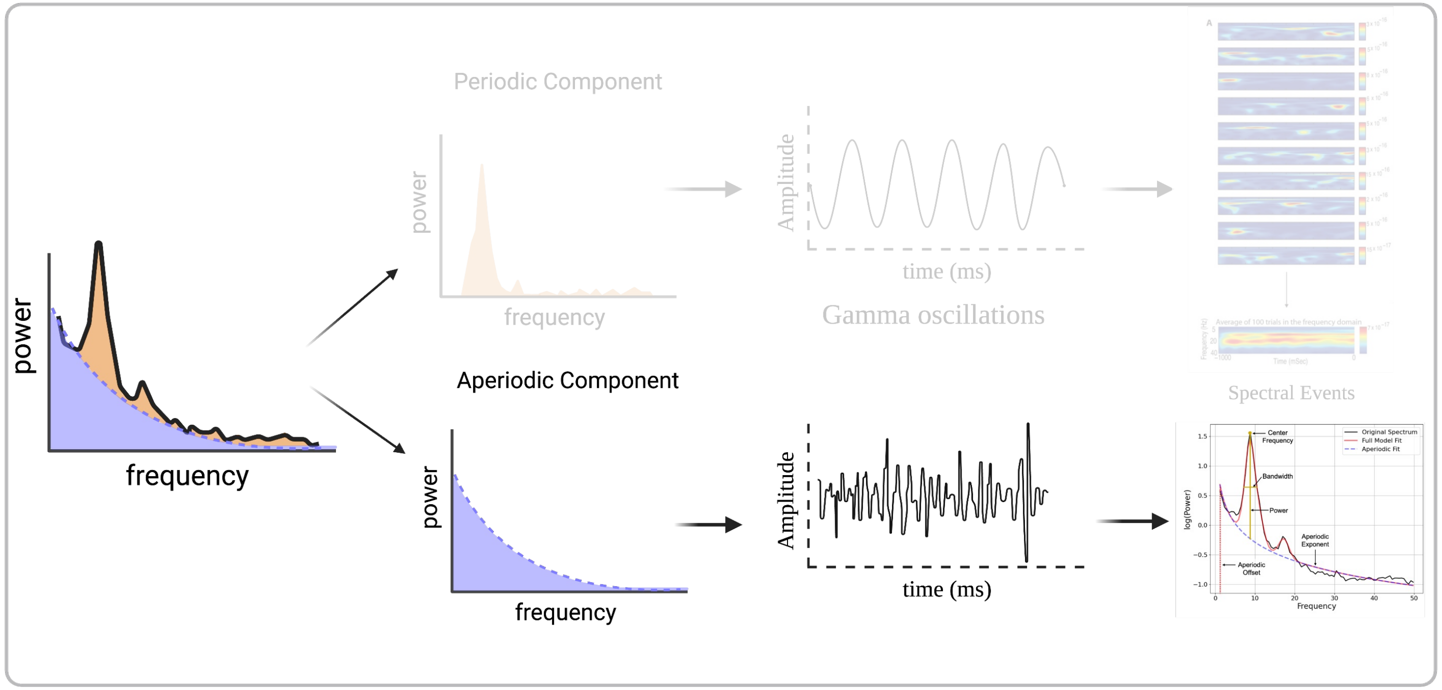
02 Mediation analyses to test whether age-related changes in EEG the Glu/GABA balance (H1.2).



Introduction



Aim 2



Aim 3

Assess EEG-derived measures of E/I balance and their associations with direct measurements of excitatory glutamate and inhibitory GABA

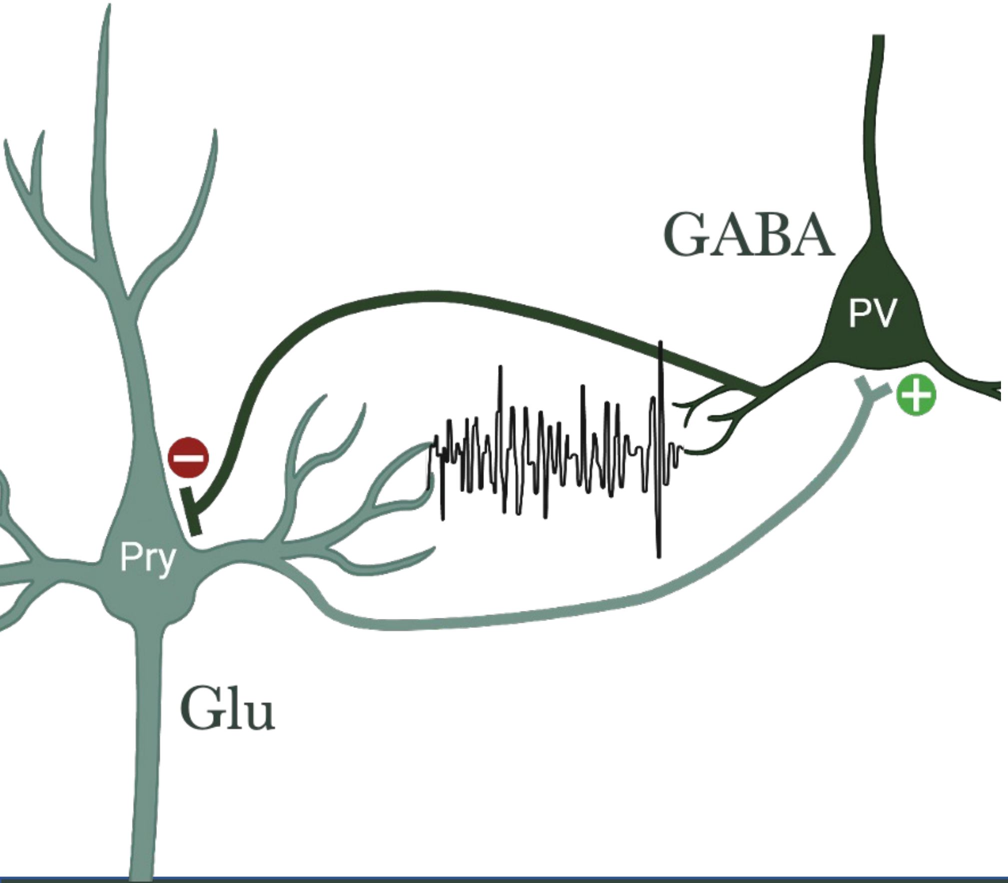
Aim 2

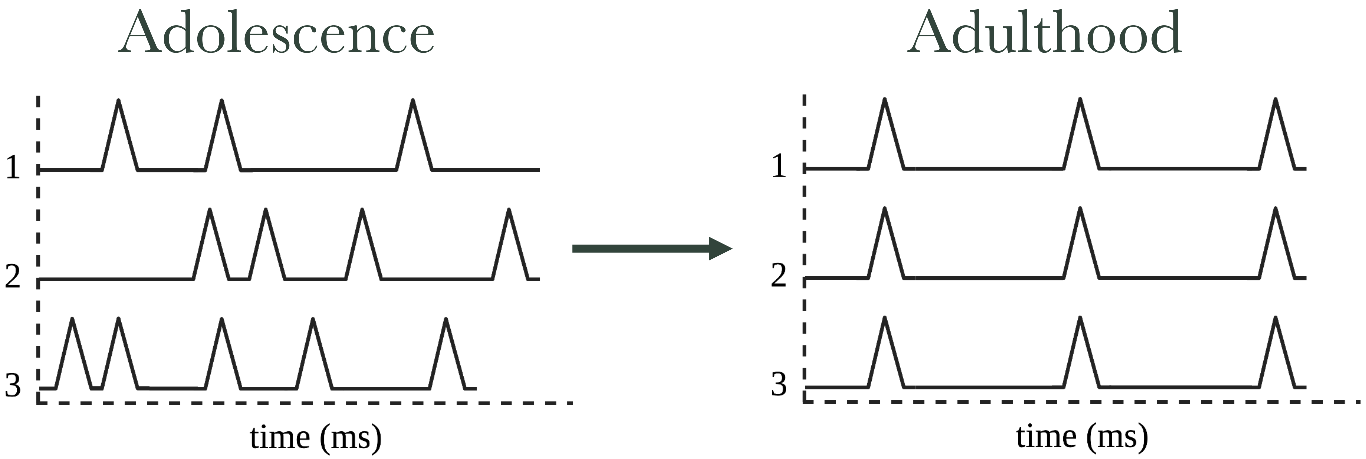
Investigate associations in DLPFC between developmental changes in **aperiodic EEG measures of E/I and MRSI evidence of E/I**

H2.1 Cortical SNR will increase with age in conjunction with developmental changes in the Glu/GABA balance

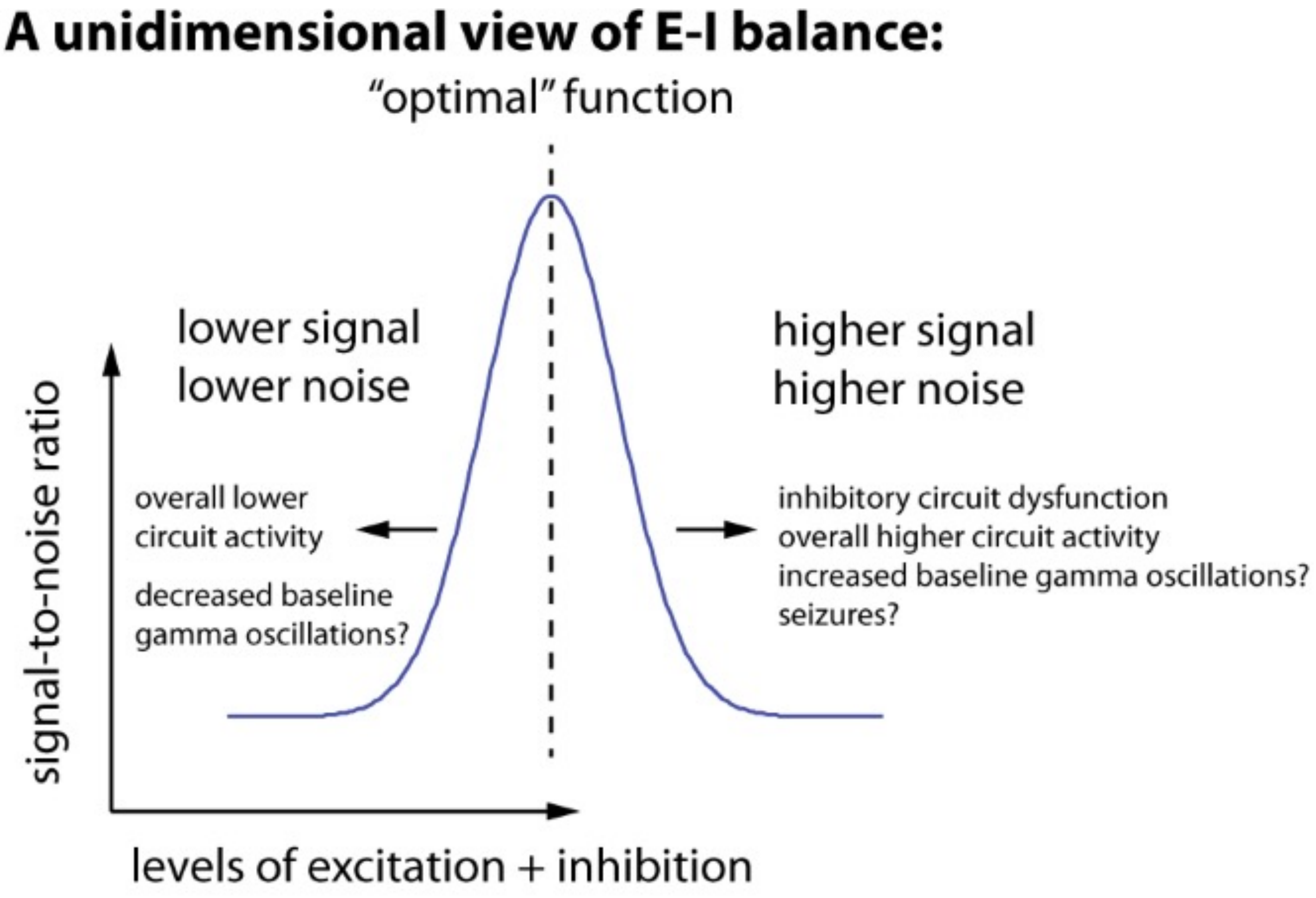
H2.2 Aperiodic EEG offset and exponent will decrease with age, indicated by decreases in broadband spectra power and a flattening of the slope, and will be mediated by developmental changes of Glu and GABA.

Synaptic interactions between PV interneurons and pyramidal support the suppression of spontaneous, asynchronous activity, in favor of evoked, synchronous firing and thus increasing SNR[1,2]



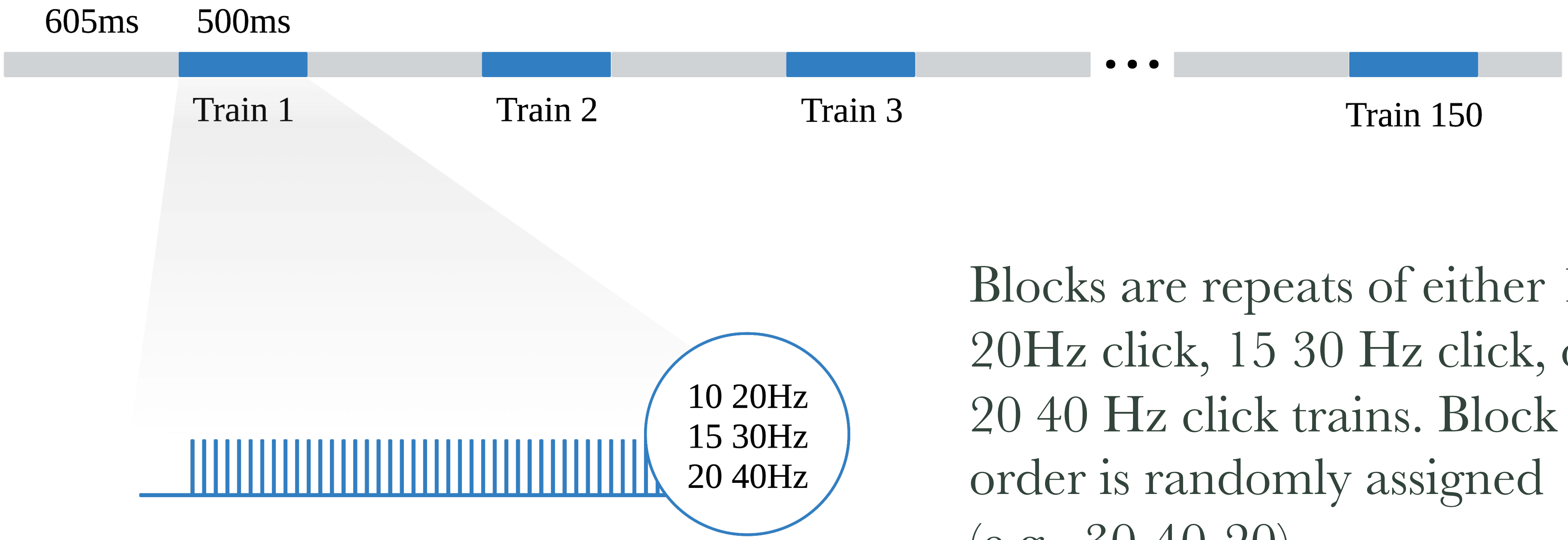


1. Toyoizumi (2013). 2. Larsen (2022)



Sohal et al, 2019

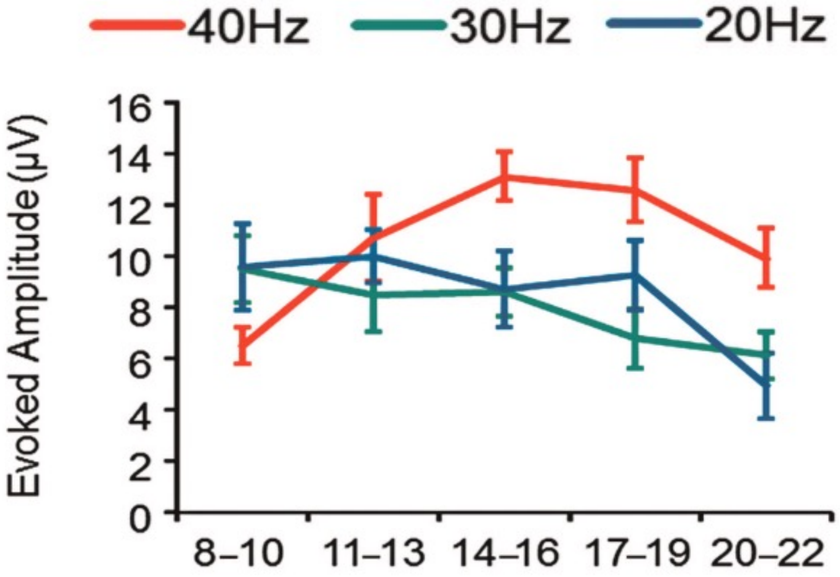
Auditory Steady State Task



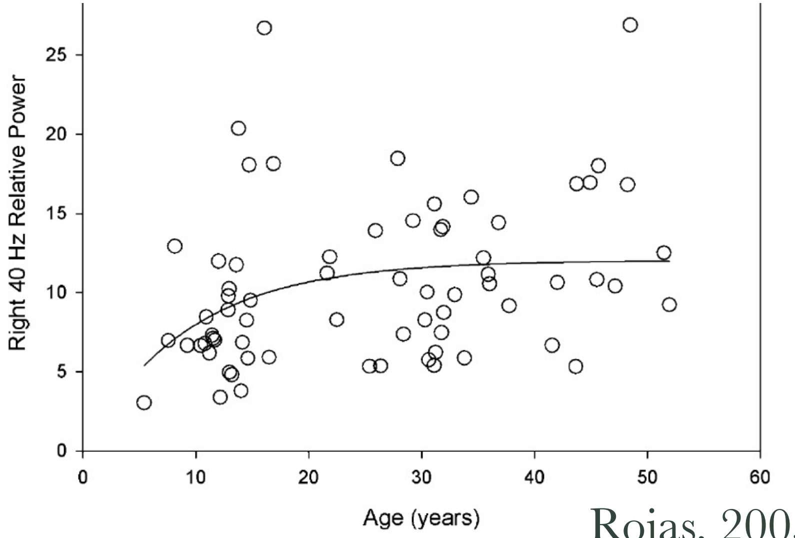
Blocks are repeats of either 10 20Hz click, 15 30 Hz click, or 20 40 Hz click trains. Block order is randomly assigned (e.g., 30-40-20).

The auditory steady state response (ASSR)

- Supported by $GABA_a$ receptors cycling between excitation inhibition[1]
- 40 Hz stimulus can be used as an indirect measure of the E/I balance[2-4]
- Significant involvement of the prefrontal cortex
- Age related increases in evoked power
- Reflect maturation of GABAergic inhibitory interneurons, spinogenesis, and synaptic pruning[5]



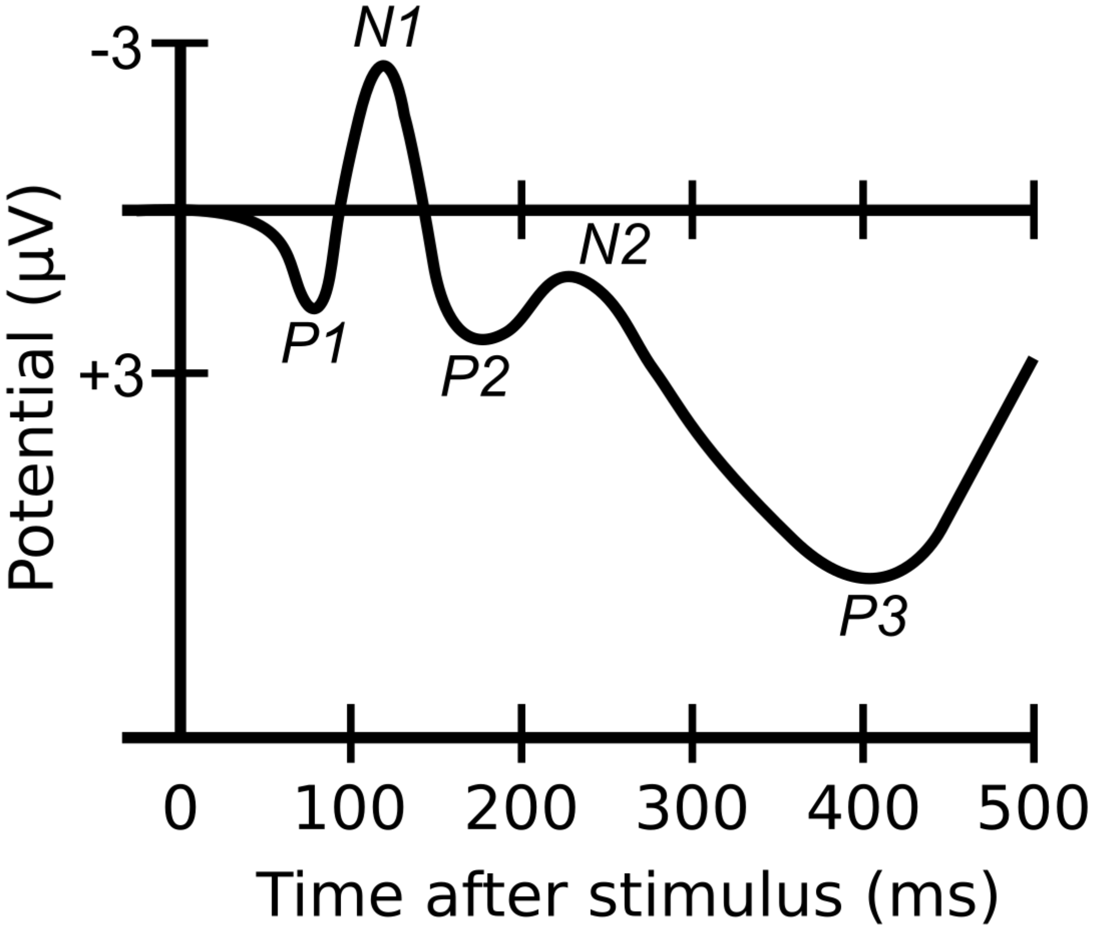
Cho, 2015



Rojas, 2005

1. Lewis (2005). 2. Gonzalez-Burgos (2008). 3. Vohs. (2010). 4. Sivarao (2016). 5. Tada (2020).

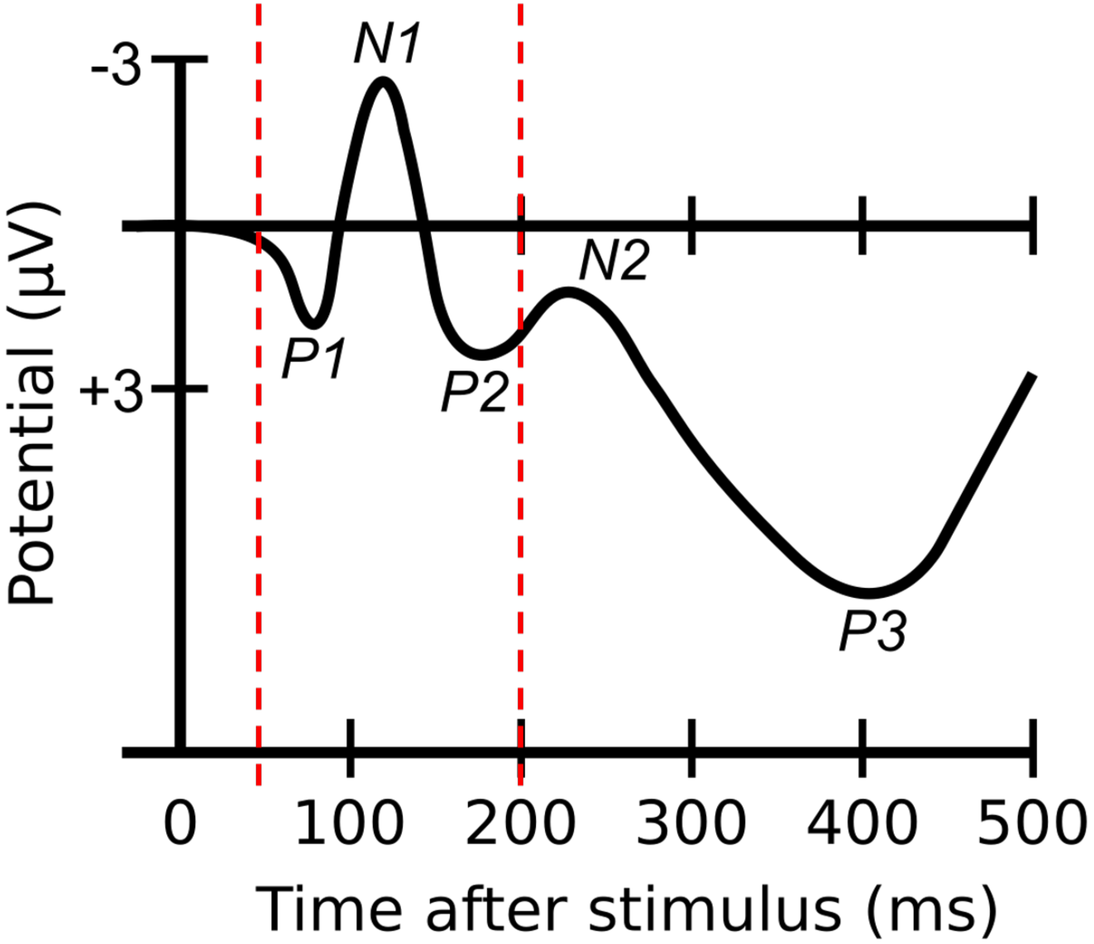
Event Related Potential



- Calculated across trials for each electrode
- Baseline corrected to the 200ms before stimulus onset.
- Time-frequency analysis
  - Wavelet transformation
  - 30 to 70Hz
  - 1 Hz intervals

1. Javitt et al. (2020). 2. Bartnik et al. (1992)

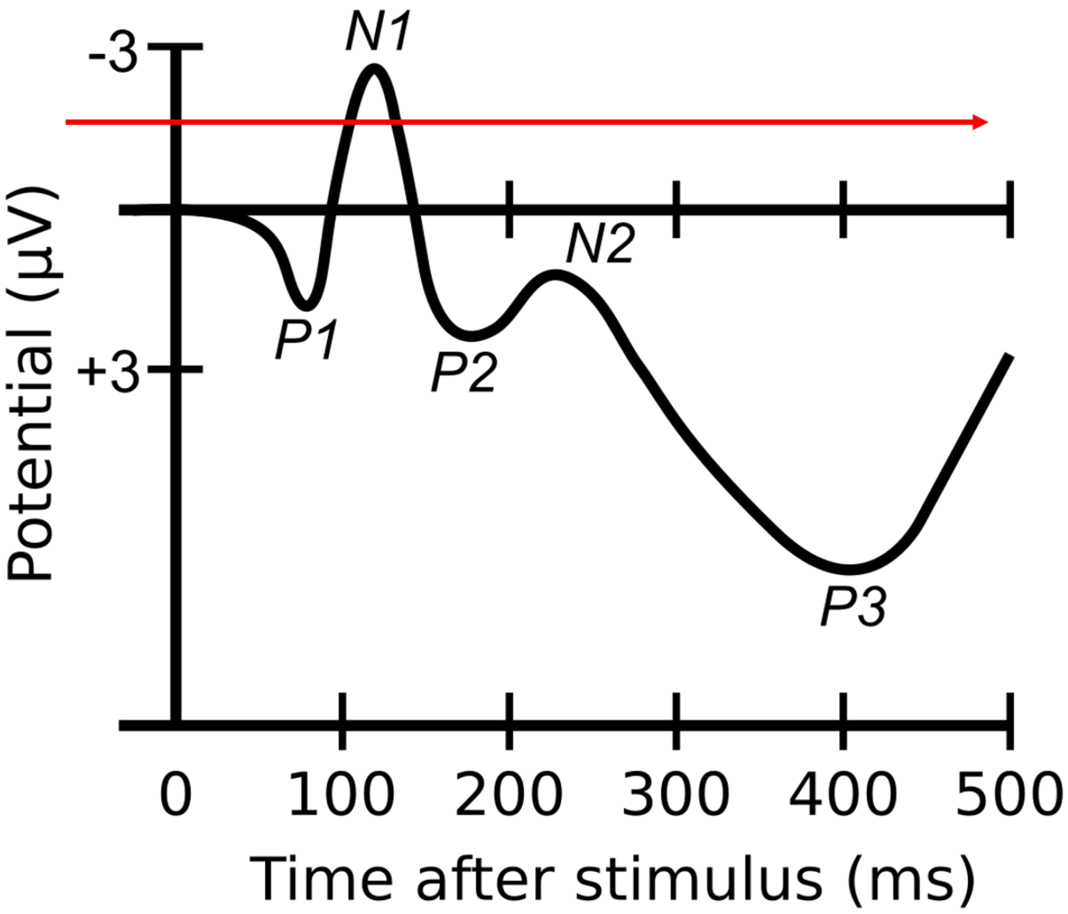
Evoked Activity



Event related spectral power (ERSP)[1] from the auditory steady state task corresponding to the 50-200ms following onset of the auditory cue

1. Delorme & Makeig. (2004)

Spontaneous Activity



Spontaneous activity will be measured as the average standard deviation of power per trial within the gamma frequency band

Cortical Signal-to-Noise Ratio (SNR)

SNR = evoked activity – spontaneous activity

01 Investigate cortical SNR across adolescence and its associations with developmental changes in the Glu/GABA balance in the same longitudinal cohort (H2.1).

Cortical SNR will increase with age in conjunction with developmental changes in the Glu/GABA balance

02 Investigate associations between EEG – derived measures of the E/I balance (the exponent and offset) and developmental changes in the Glu/GABA balance (H2.2).

Aim 2: Next Steps & Expected Outcomes

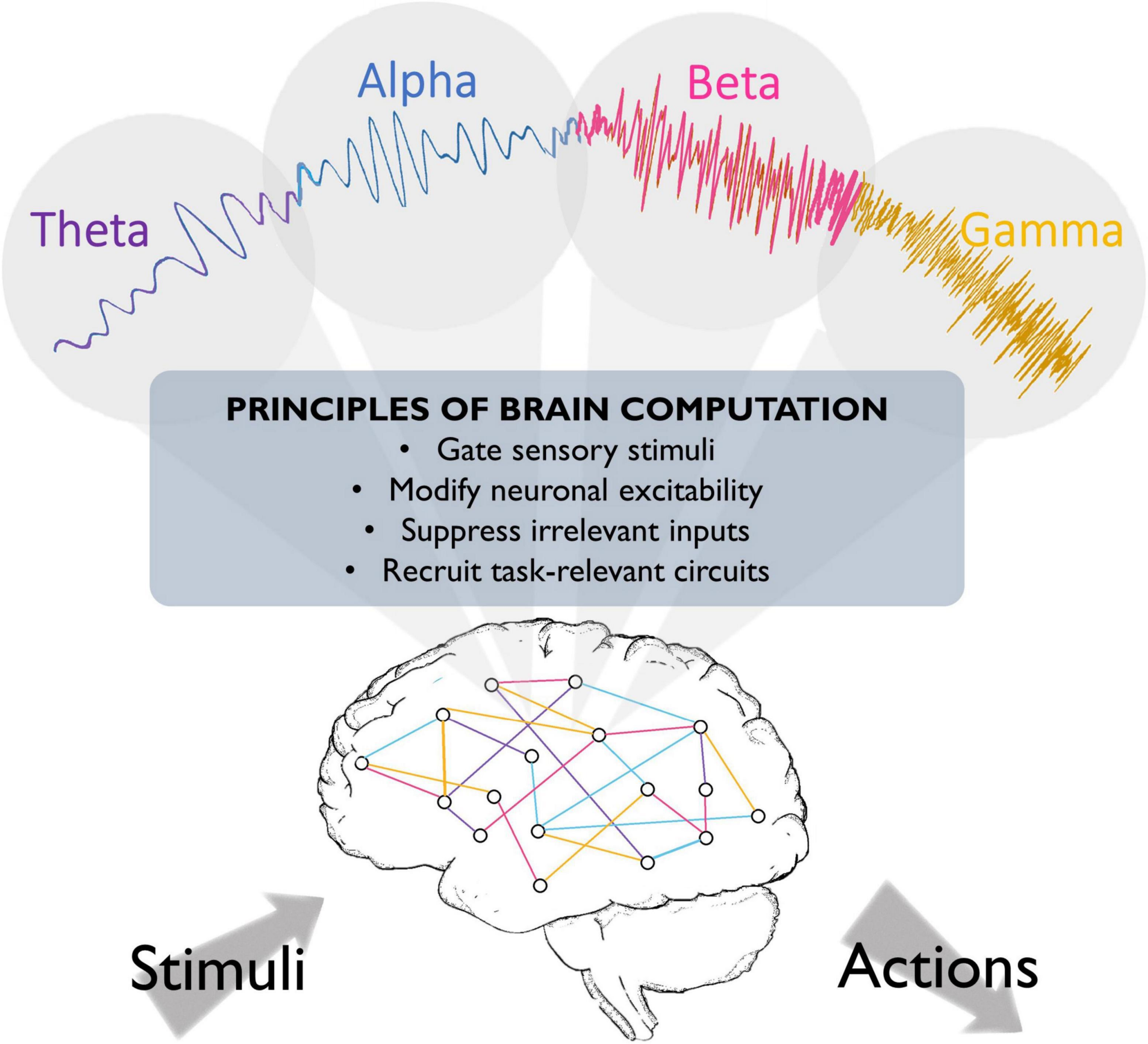
Assess EEG-derived measures of E/I balance and their associations with direct measurements of excitatory glutamate and inhibitory GABA

Aim 2

Investigate associations in DLPFC between developmental changes in **aperiodic EEG measures of E/I and MRSI evidence of E/I**

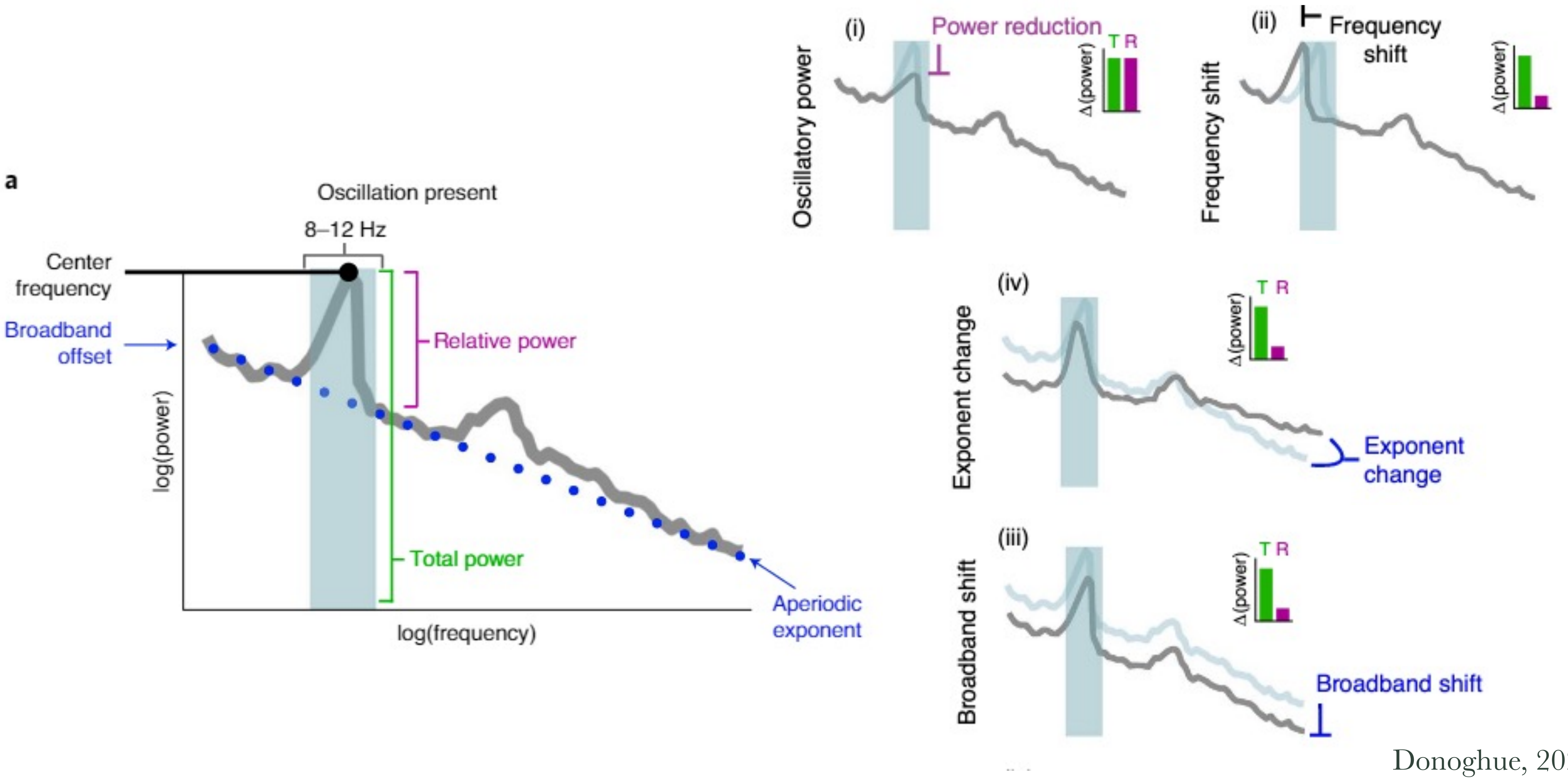
H2.1 Cortical SNR will increase with age in conjunction with developmental changes in the Glu/GABA balance

H2.2 Aperiodic EEG offset and exponent will decrease with age, indicated by decreases in broadband spectra power and a flattening of the slope, and will be mediated by developmental changes in the Glu/GABA balance.



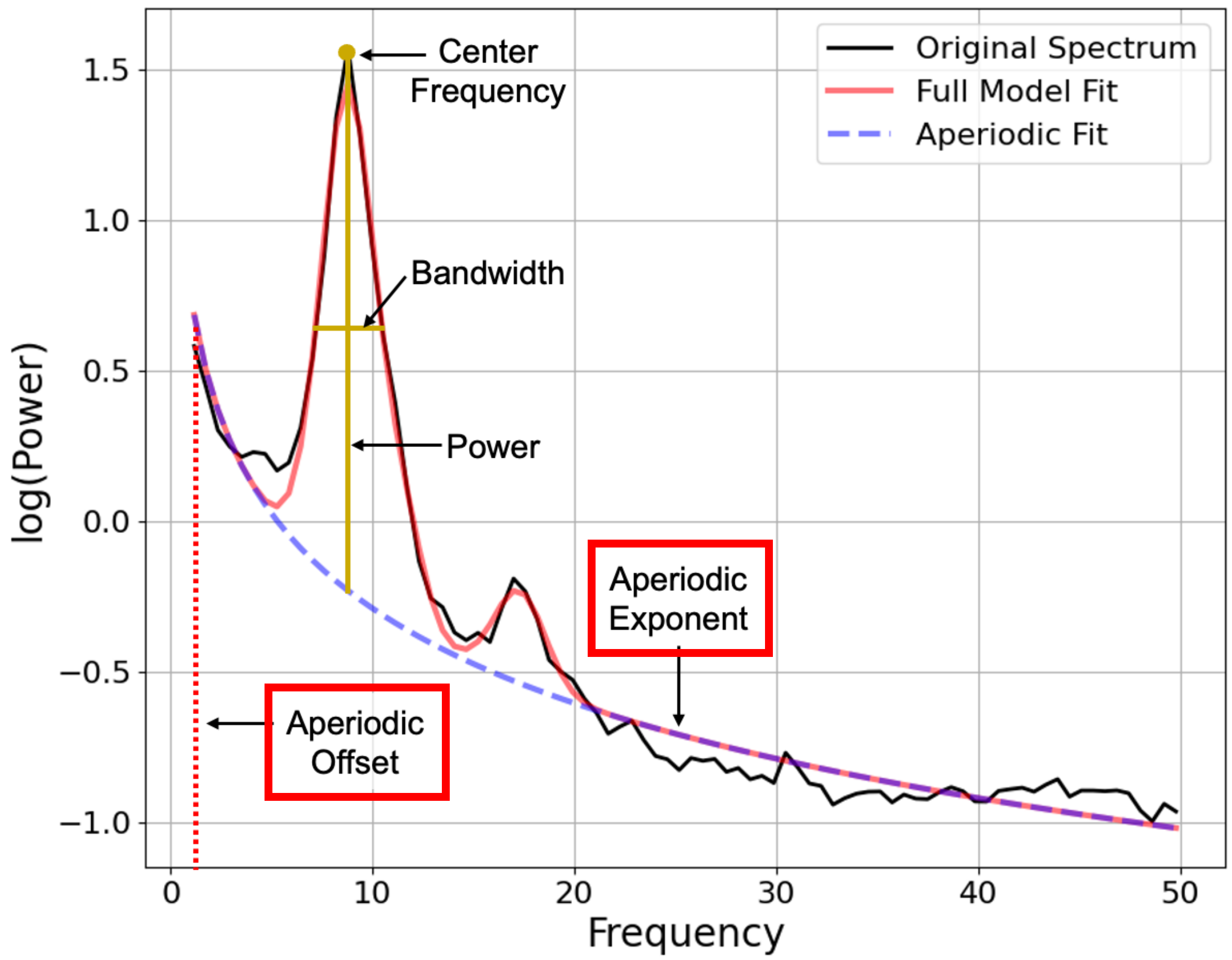
Ibarra-Lecue, 2022

Aim 2: Background



Donoghue, 2020

Aim 2: Background



The steepness, or exponent, has been linked to shifts in the E/I balance[1-8]

- Lower exponent → more balance
- Higher exponent → less balance

Offset is thought to reflect broadband shifts in power

- Neuronal population spiking[9-10]

Associated with WM task performance[11]

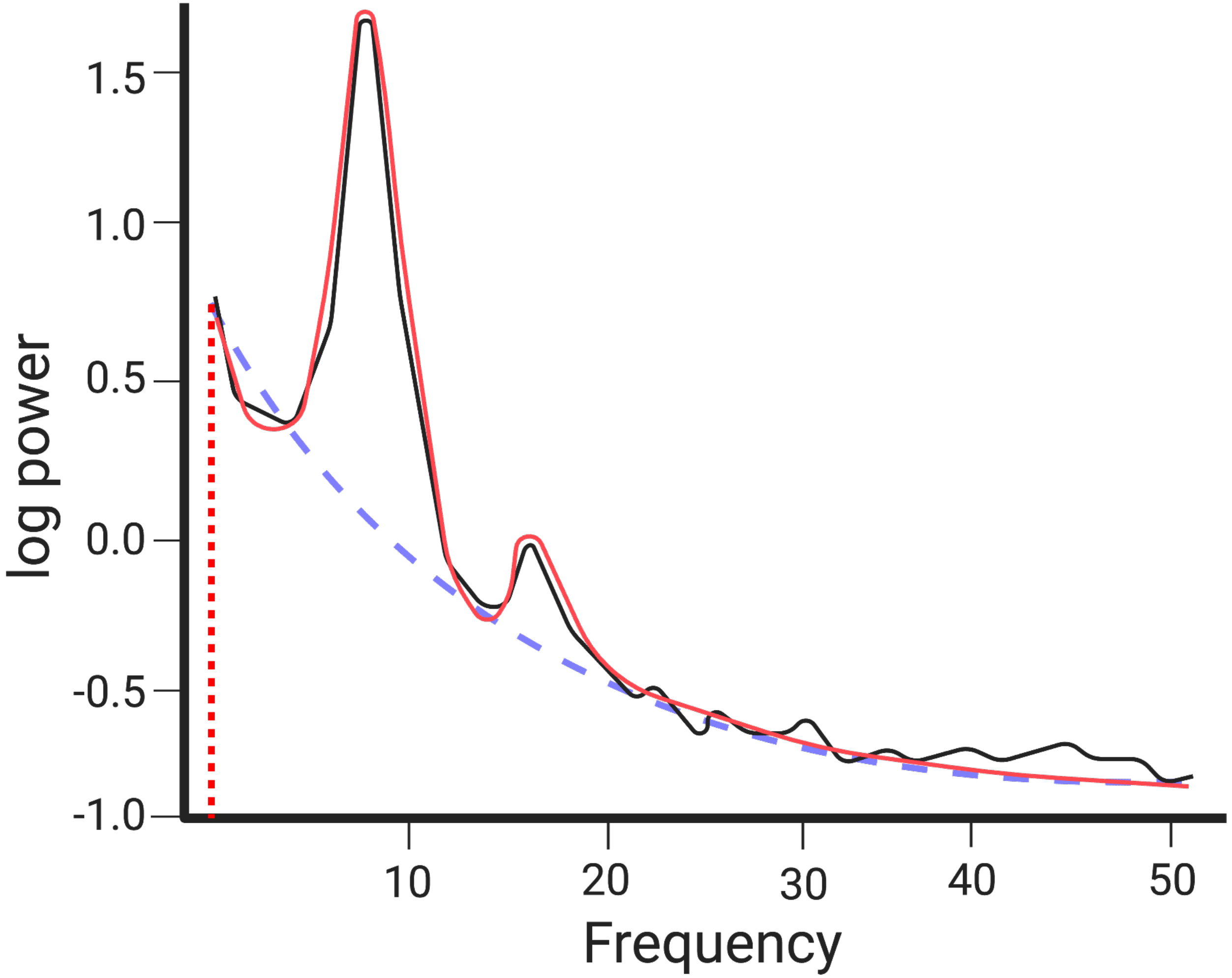
Shown to be altered in disease states, including schizophrenia [8]

Aim 2: Background

1. Molina (2020). 2. Ostlund (2021). 3. Robertson (2019). 4. Gao (2017). 5. Donoghue (2020). 6. Zhang (2011). 7. Mamuya (2021). 8. Voytek (2015). 9. Manning (2009). 10. Miller (2014) 11. Podvalny (2015)

Flattening of the aperiodic exponent from childhood to young adulthood[1-4]

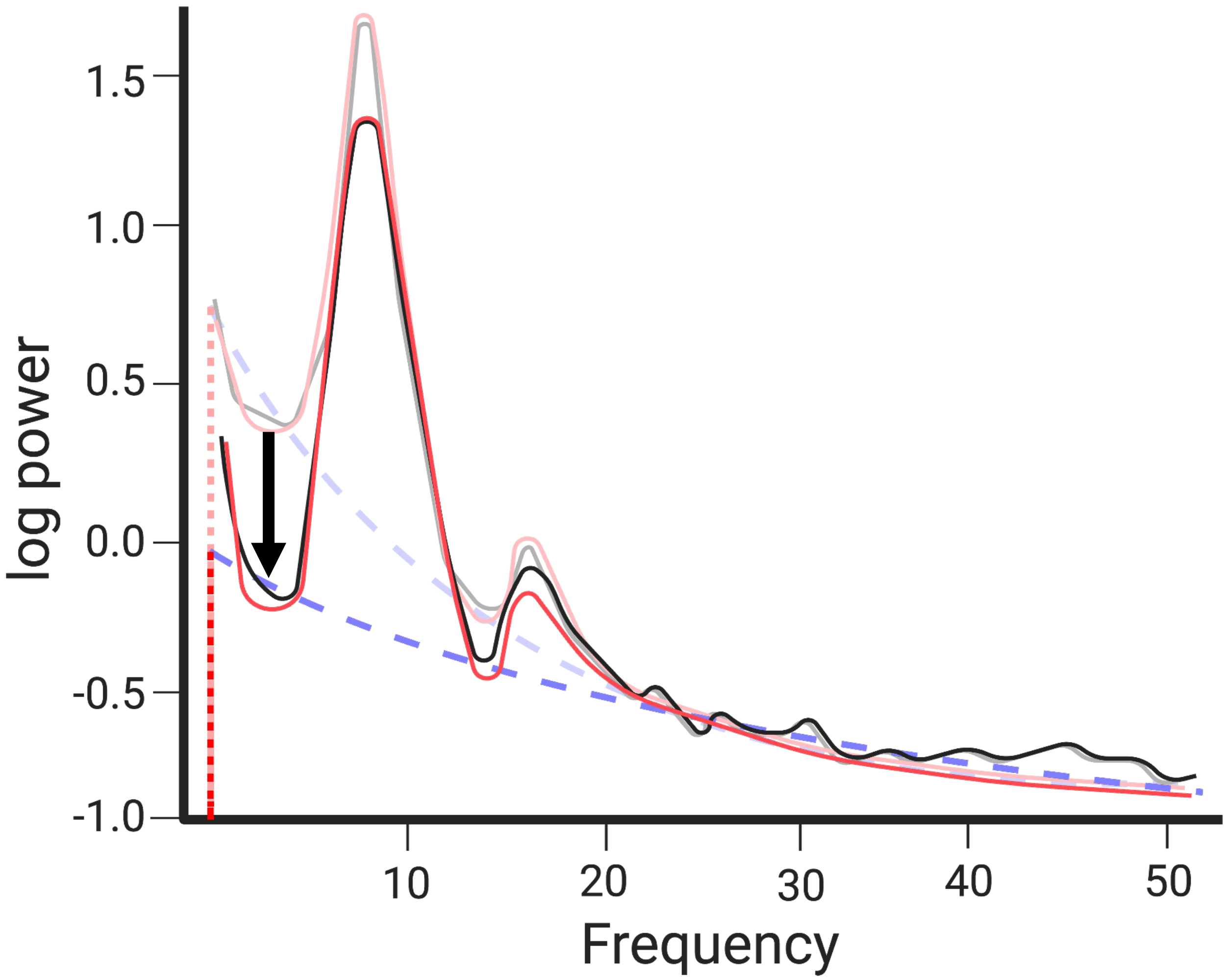
Childhood



1. Hill (2022). 2. McSweeney (2021). 3. Trondle (2022). 4. Cellier, (2021). 5. Voytek (2015)

Flattening of the aperiodic exponent from childhood to young adulthood[1-4]

Adulthood



1. Hill (2022). 2. McSweeney (2021). 3. Trondle (2022). 4. Cellier, (2021). 5. Voytek (2015)

We will assess aperiodic EEG activity in a large longitudinal dataset and its associations with MRSI derived measures of the Glu/GABA balance

Resting State

Participants will maintain a central fixation using a white fixation cross

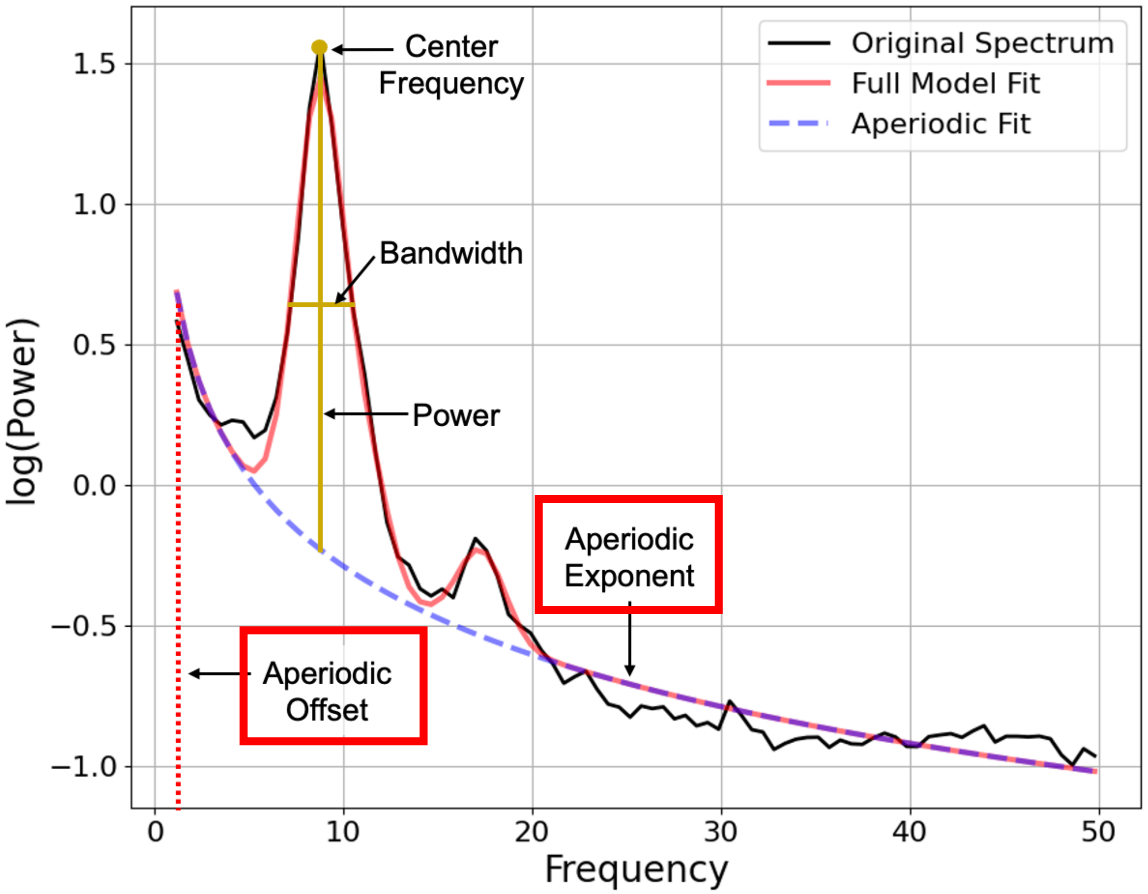
8 mins total

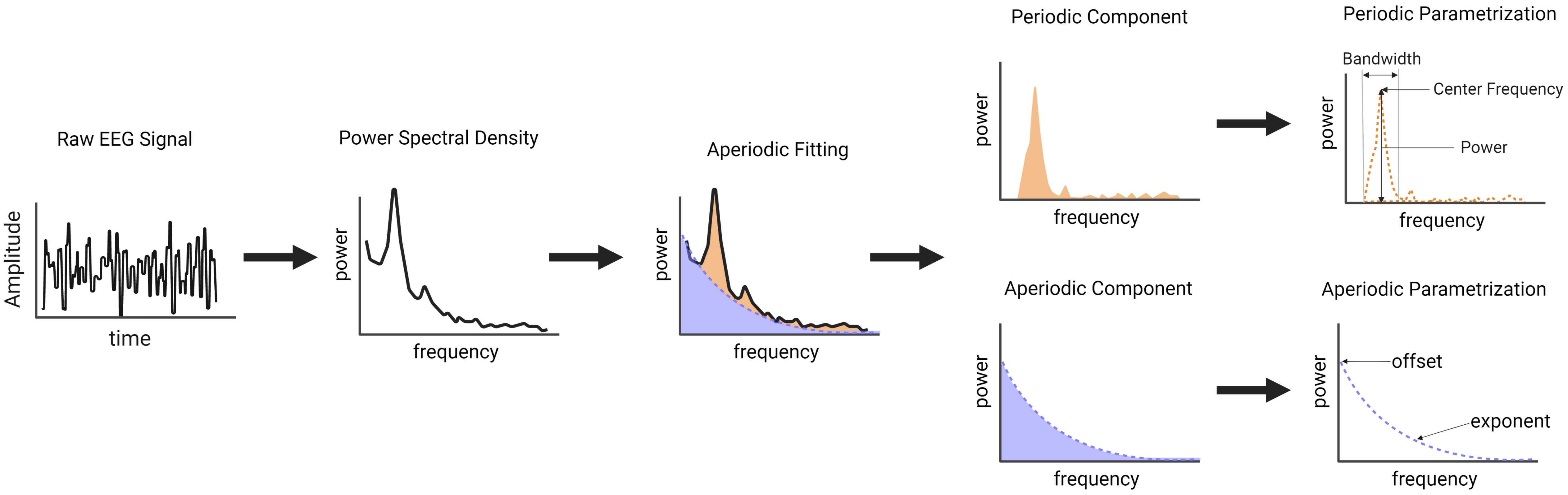
Randomly alternating between eyes open and eyes closed

Aperiodic *1/f* Activity

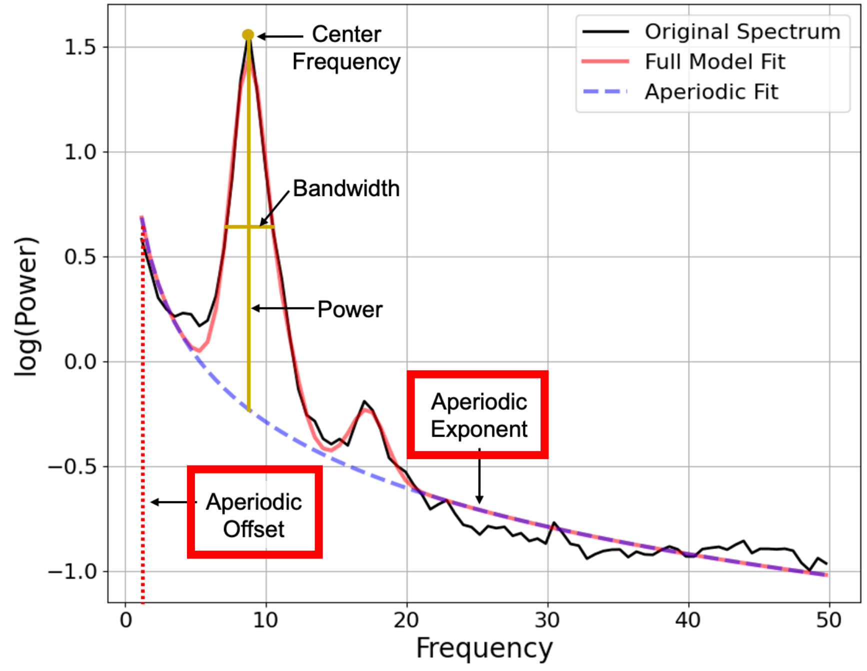
Power spectral density (PSD) will be first calculated separately for each participant and electrode across the continuous EEG using Welch's method implemented in MATLAB (2 s Hamming window, 50% overlap).

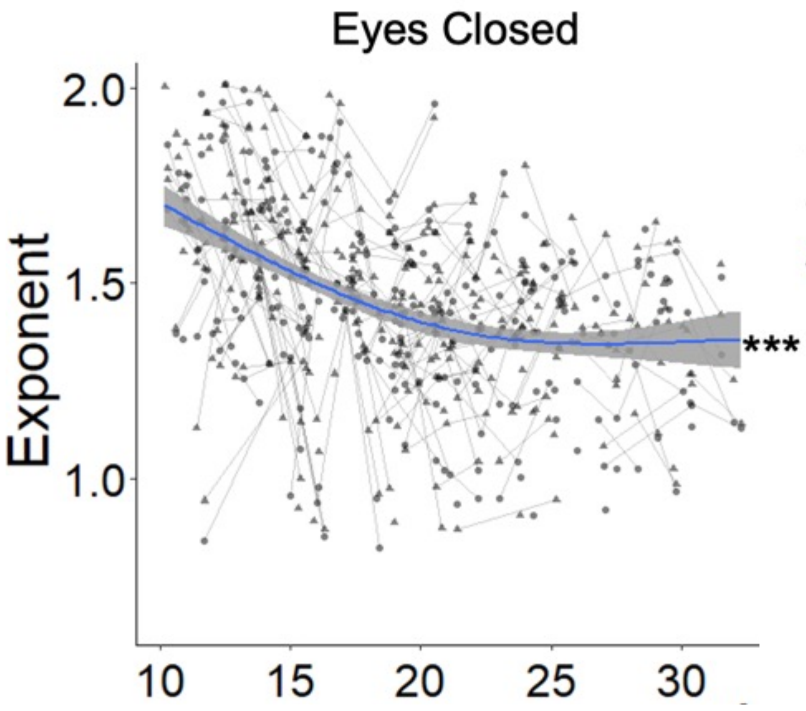
The Fitting Oscillations and One Over *f* (FOOOF) python toolbox

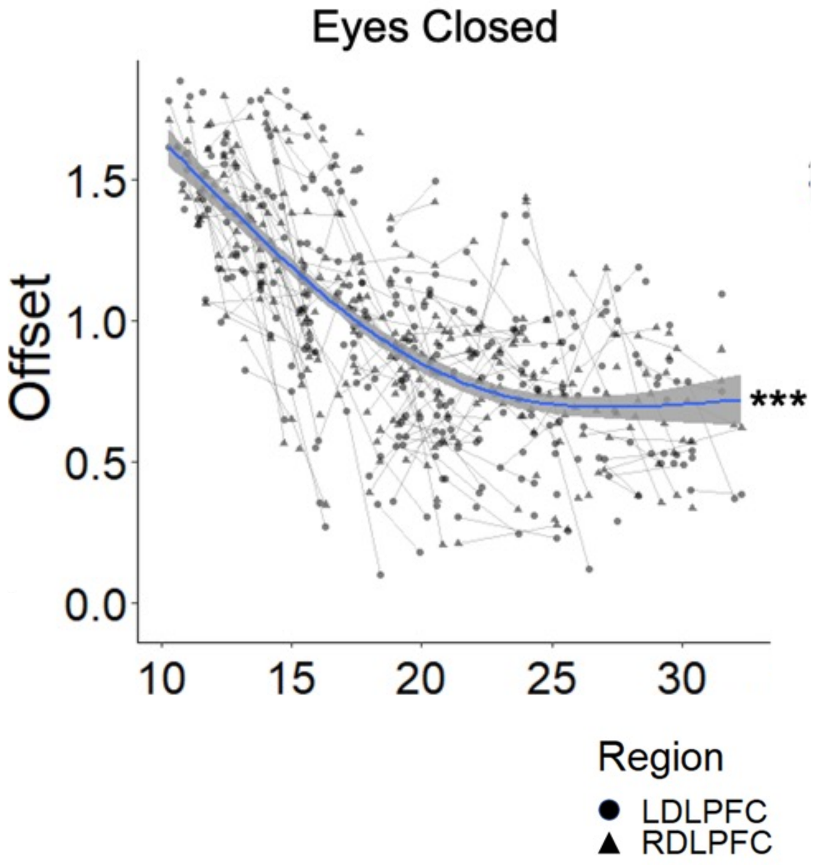




Aim 2: Methods







Aim 2: Preliminary Results

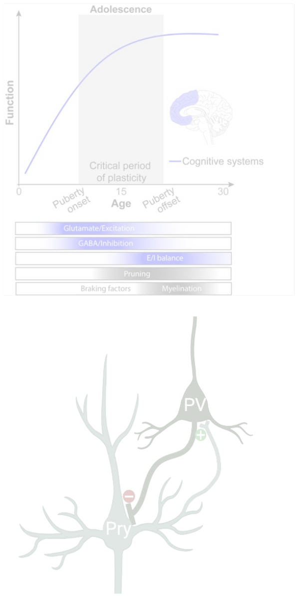
01 Investigate cortical SNR across adolescence and its associations with developmental changes in GABA and Glu (H2.1).

Cortical SNR will increase with age in conjunction with developmental changes in Glu and GABA

02 Investigate associations between EEG – derived measures of the E/I balance (the exponent and offset) and developmental changes in the Glu/GABA balance (H2.2).

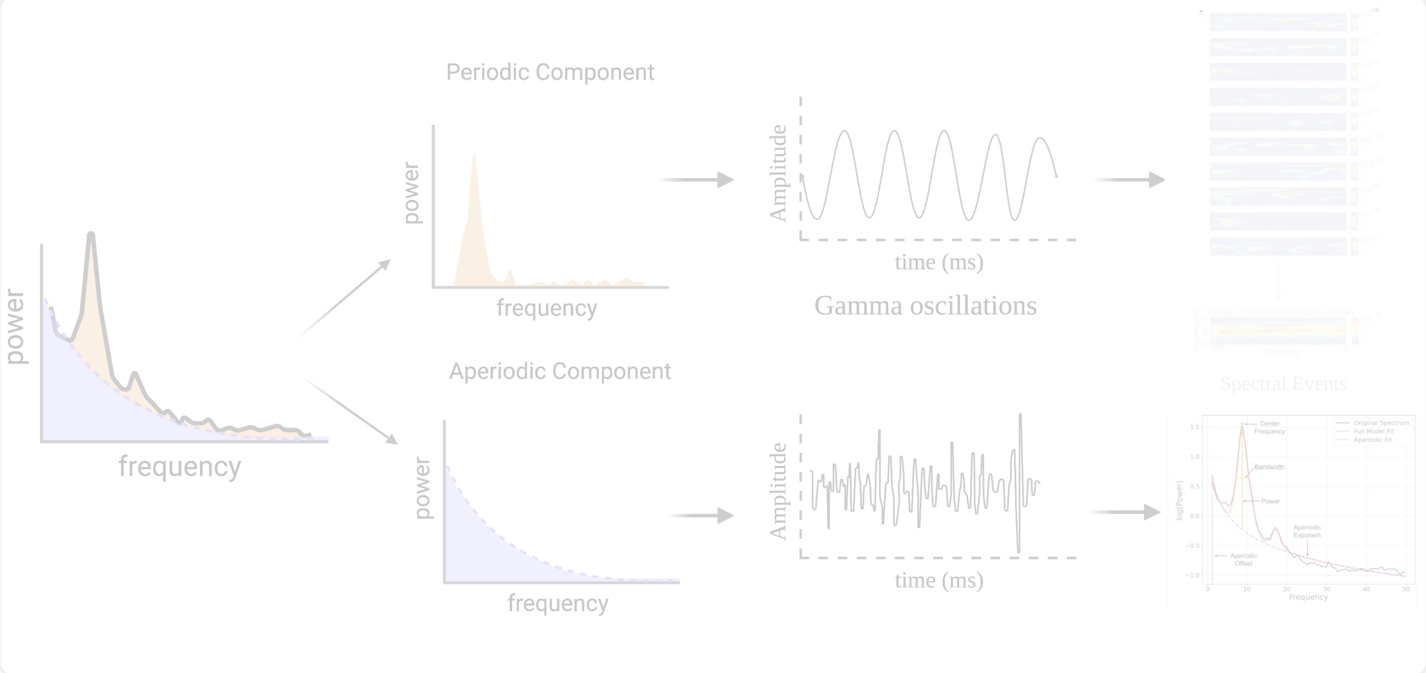
Aperiodic EEG offset and exponent will be mediated by developmental changes in the Glu/GABA balance

Introduction

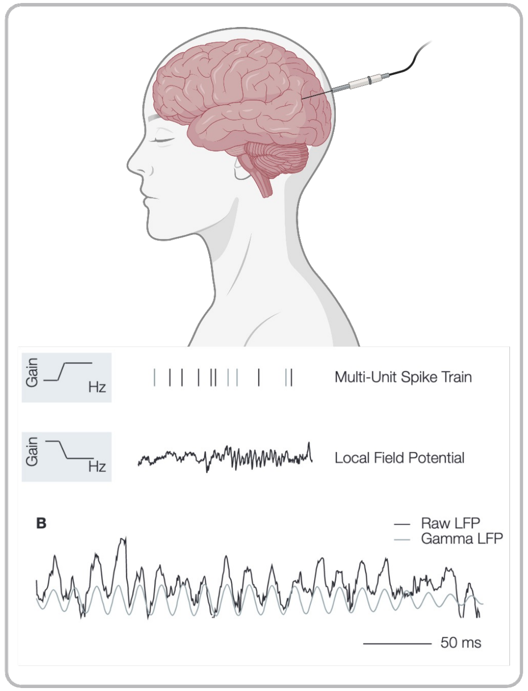


PV+ PN Circuitry

Aim 2



Aim 3



Stereoelectroencephalography (sEEG)

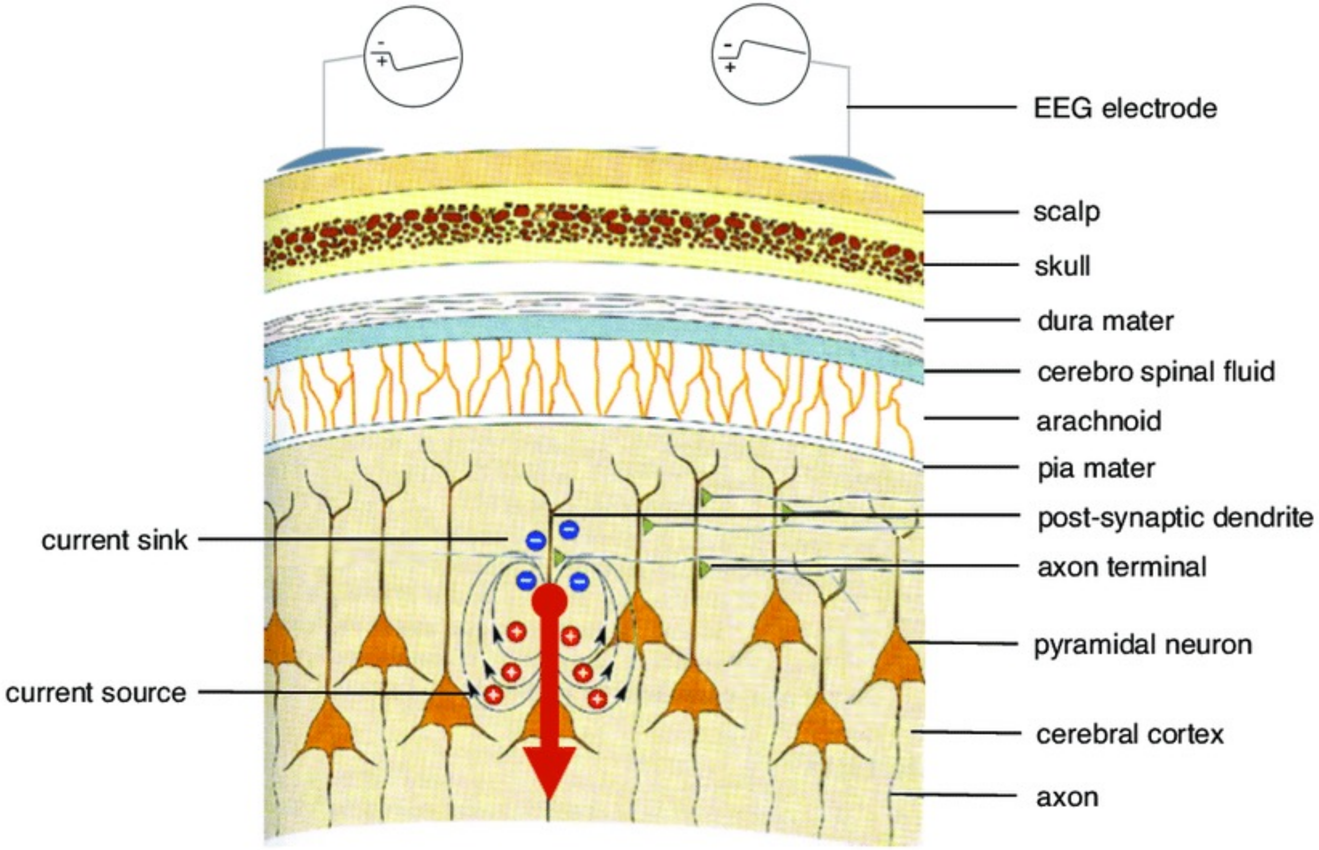
Interrogate whether global developmental changes seen in scalp EEG are present when leveraging the greater spatial and temporal resolution of sEEG

Aim 3

Characterize **properties of neural activity** underlying developmental changes in EEG Measures of E/I using **sEEG**

H3.1 High gamma and gamma band power will decrease across adolescence.

H3.2 sEEG will demonstrate comparable developmental changes in E/I balance in cortical regions as those found in whole brain EEG. Aperiodic offset derived from the LFP will be associated with firing rate, informing neuronal population spiking



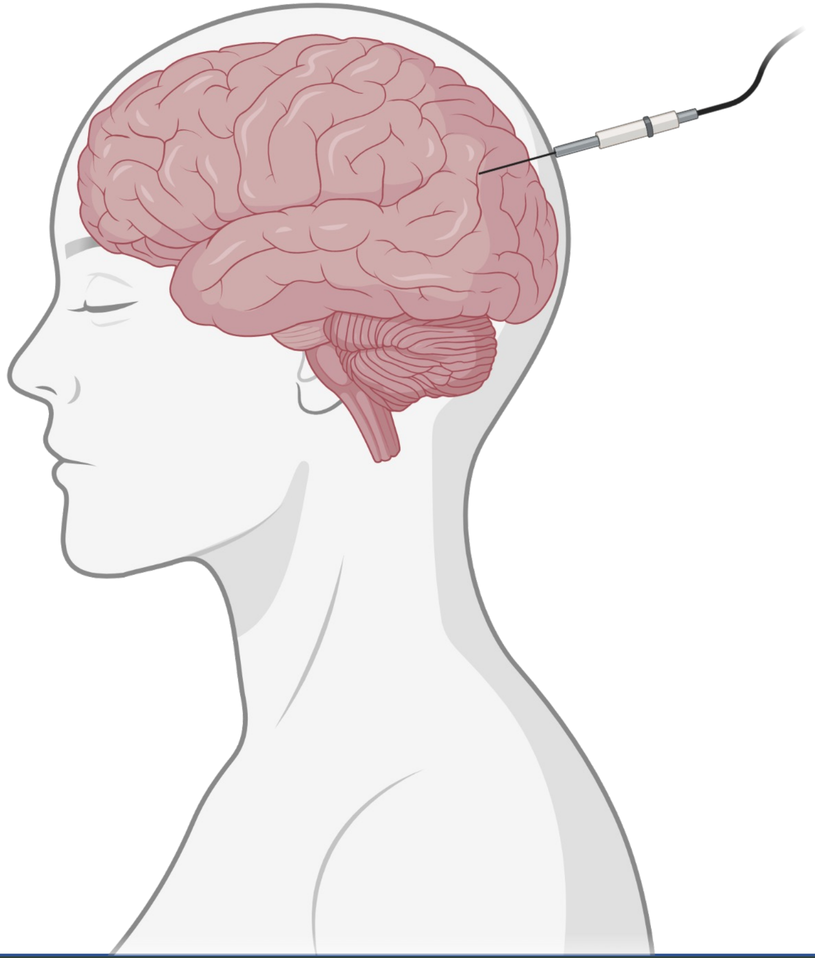
EEG is
- Non-invasive
- Can be applied to large normative populations

However
- Signal that is recorded on the scalp
- Limiting our understanding of source and direct neural function and restricting to assessment of the cortical surface

Stereoelectroencephalography (sEEG)

- Record neural activity during cognitive tasks or are at rest
- Provides a direct rendering of neural function
- Can inform the basis of the non-invasive EEG approach

High gamma power (>80 Hz) is tightly correlated with spiking activity[1-4]



1. Manning (2009). 2. Ray (2011). 3 Crone (2009). 4. Jacabs and Kahana (2010)

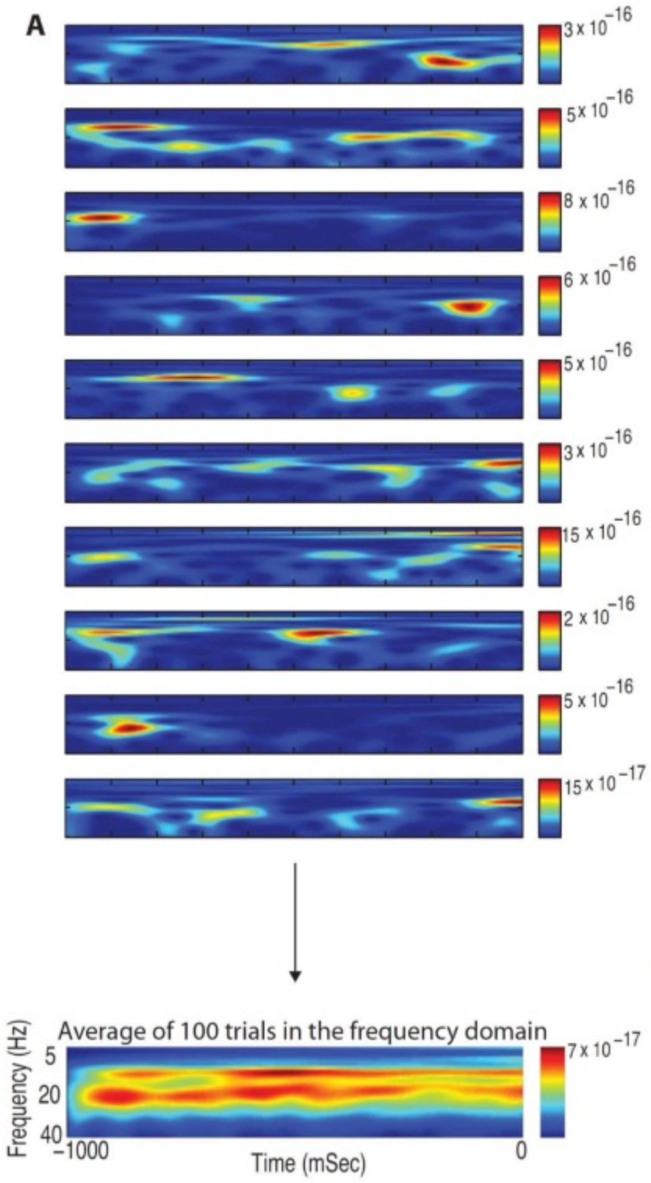
Participants

Dataset comprised of pediatric epilepsy patients

Based on numbers from 2019, we expect approximately 5-10 10-25yo patients without cognitive impairment per year

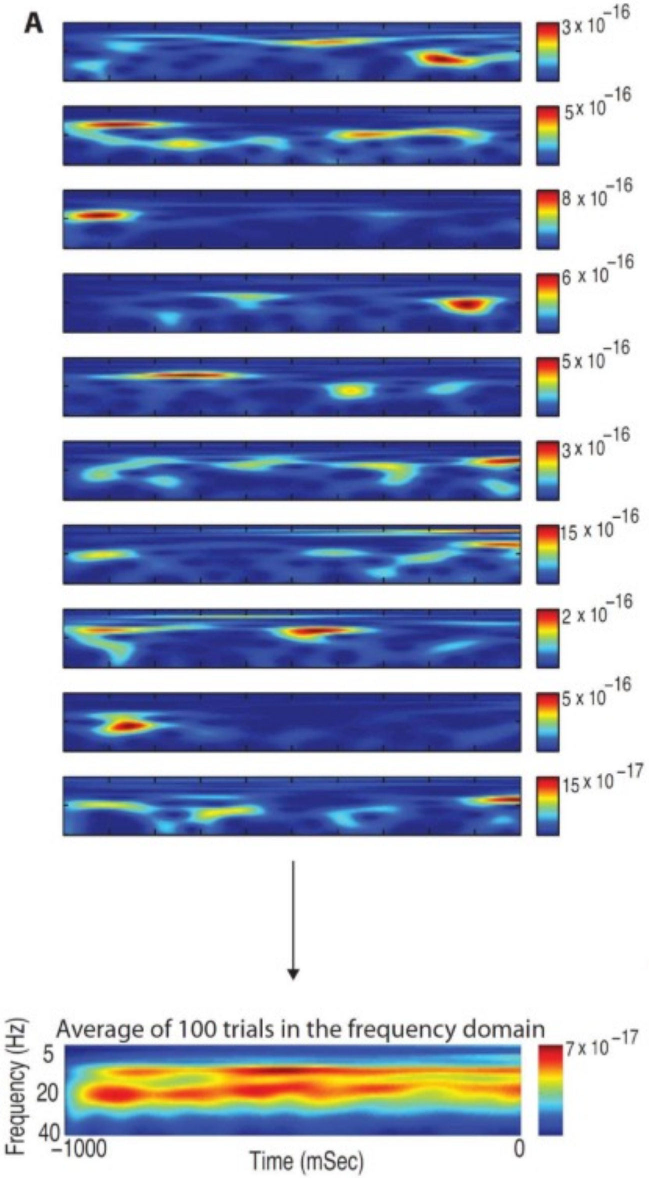
Regions of coverage vary on seizure localization

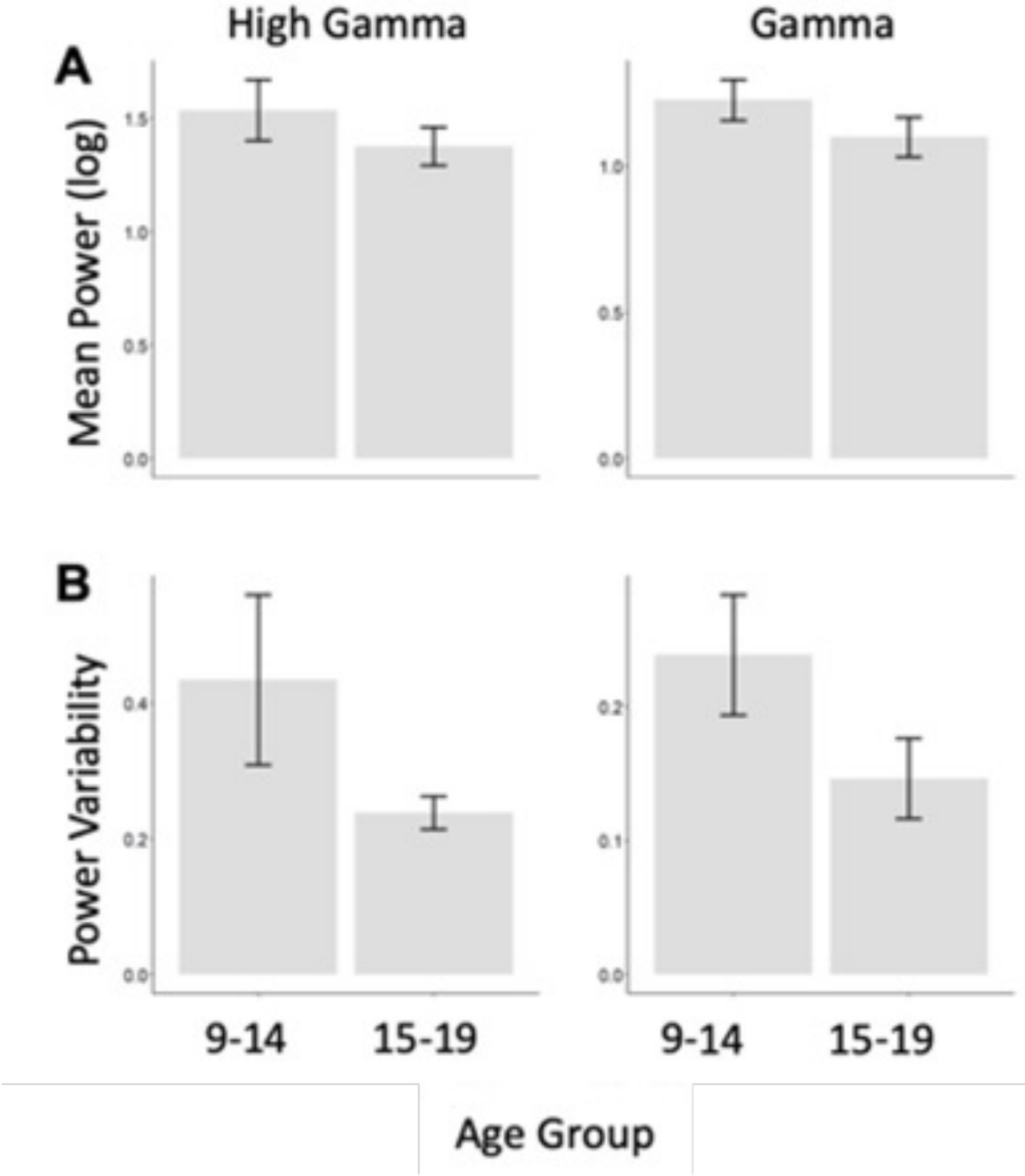
Resting state sEEG data has been collected in 13 participants, ages 9-21.



Spectral Event Analysis

- Within region, spectral events analysis, as seen in scalp EEG (Aim 1), will be adapted to the sEEG resting state data to derive measures of discrete oscillatory events, including the average power and number of events
  - Gamma (30 – 75 Hz) and High Gamma (75 – 150 Hz)





Aim 3: Preliminary Results

01 Continue to assess spectral events on the cortical level in the gamma and high gamma frequency bands (H3.1).

Spectral event power and number of events will decrease with age

02 Assess aperiodic components of invasive sEEG that may be more indicative of neuronal population spiking and provide insight to critical period plasticity

Aperiodic components corresponding to gamma and high gamma will have strong developmental changes across adolescence that may be more indicative of the E/I balance compared to broadband aperiodic components.

Interrogate whether global developmental changes seen in scalp EEG are present when leveraging the greater spatial and temporal resolution of sEEG

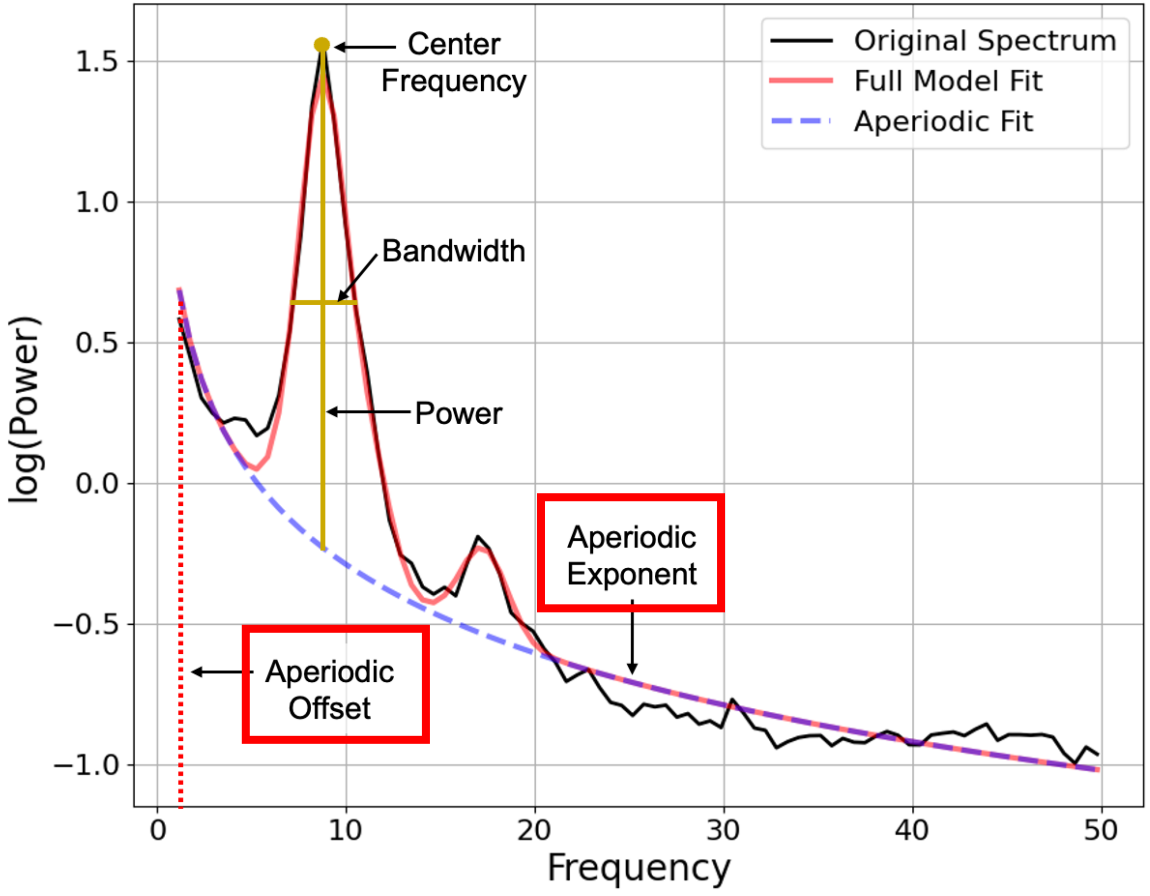
Aim 3

Characterize **properties of neural activity** underlying developmental changes in EEG Measures of E/I using **sEEG**

H3.1 High gamma and gamma band power will decrease across adolescence.

H3.2 sEEG aperiodic offset derived will be associated with high gamma power, informing neuronal population spiking

Aperiodic *1/f* Activity



Oscillatory component of the signal in the gamma (30 – 70 Hz) and high gamma (75 – 150 Hz) frequency bands will be assessed for developmental changes

Associations between 1/f offset and high gamma power will be tested to investigate the offsets associations with neuronal population spiking

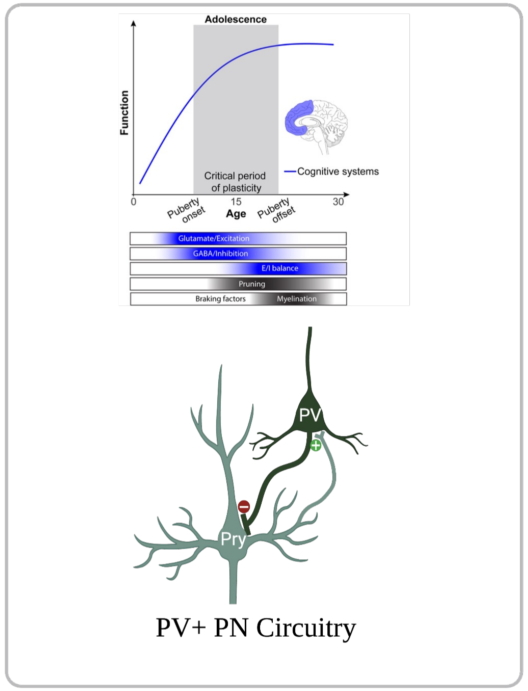
01 Continue to assess spectral events on the cortical level in the gamma and high gamma frequency bands (H3.1).

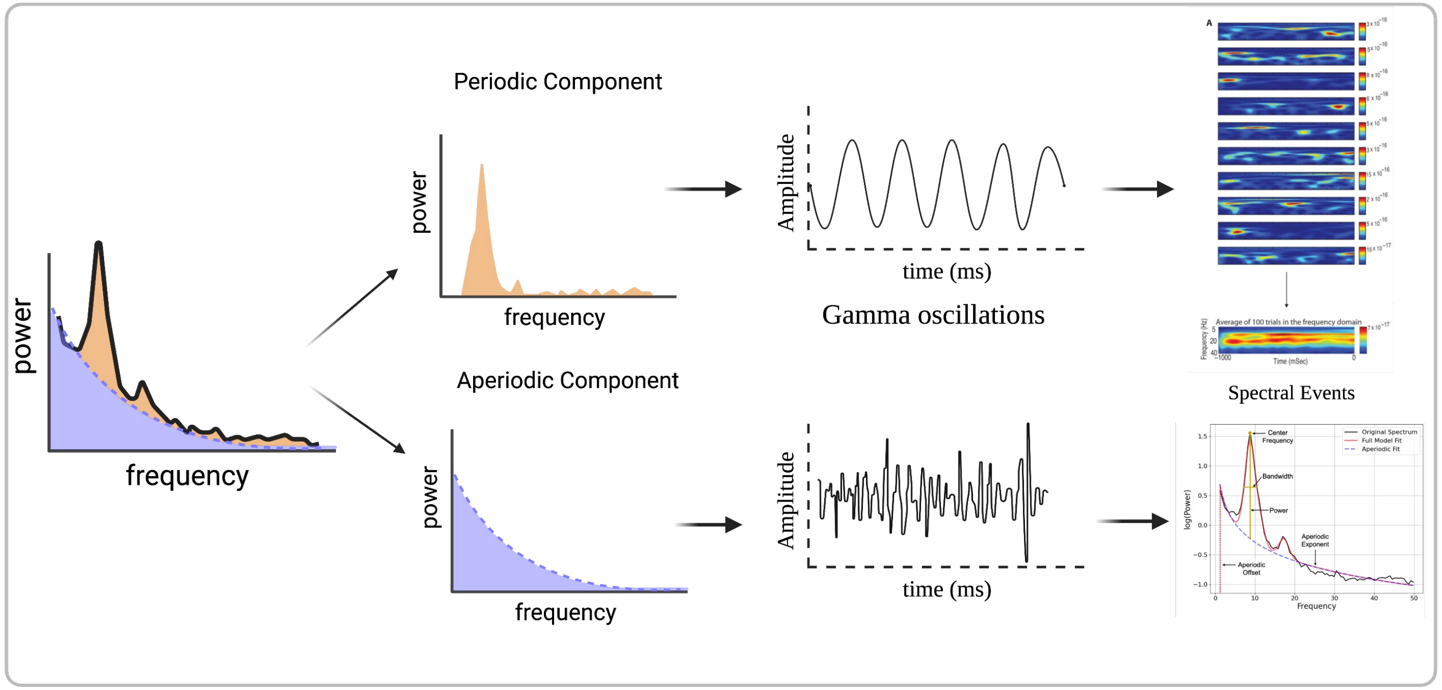
Spectral event power, number of events, and duration will decrease with age

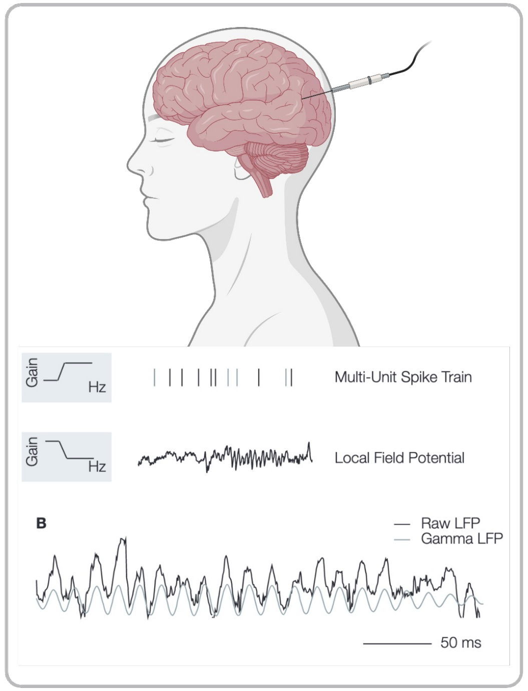
02 Assess aperiodic components of invasive sEEG that may be more indicative of neuronal population spiking and provide insight to critical period plasticity

Aperiodic components corresponding to gamma and high gamma will have strong developmental changes across adolescence that may be more indicative of the E/I balance compared to broadband aperiodic components.

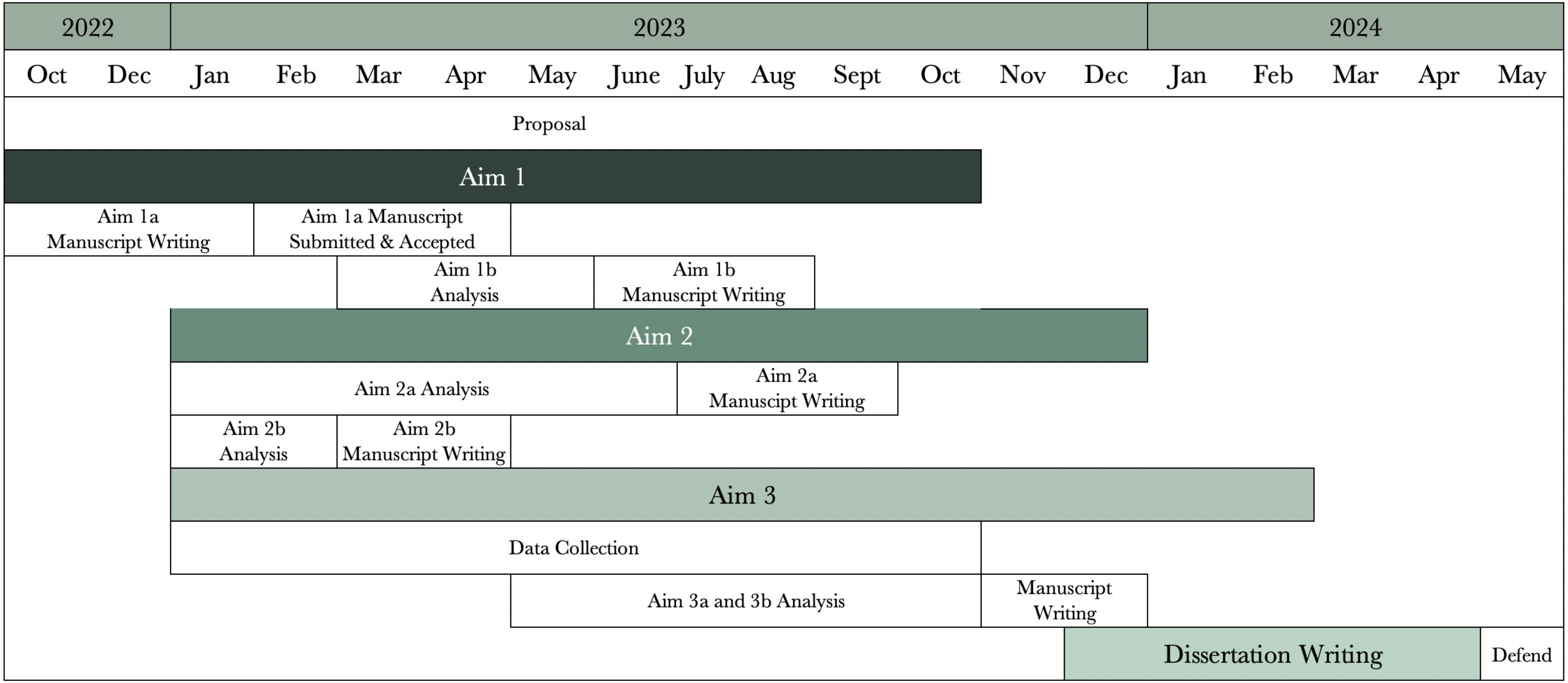
sEEG aperiodic offset will be associated with high gamma power


Adolescence
Function
Critical period of plasticity
Cognitive systems
0
15
30
Puberty onset
Age
Puberty offset
Glutamate/Excitation
GABA/Inhibition
E/I balance
Pruning
Braking factors
Myelination
PV
Pry
PV+ PN Circuitry


power
frequency
Periodic Component
power
frequency
Aperiodic Component
power
frequency
Amplitude
time (ms)
Gamma oscillations
Amplitude
time (ms)
Spectral Events
Frequency


Gain
Hz
Multi-Unit Spike Train
Gain
Hz
Local Field Potential
B
Raw LFP
Gamma LFP
50 ms

Timeline and Publications *



Aim 1 Manuscripts

Spectral events and WM (published)
Spectral events and MRSI

Aim 2 Manuscripts

FOOOF vs MRSI (in prep)
SNR vs MRSI

Aim 3 Manuscripts

sEEG developmental findings

* Optimistic and Ambitious Estimations

Acknowledgements

Beatriz Luna, PhD
Finn Calabro, PhD
Will Foran, MS
Orma Ravindranath – PhD Candidate
Maria Perica – PhD Candidate
Amar Ojha – PhD Candidate
Sam Elliot – PhD Candidate
Matt Misar – Research Assistant Alumni
Alyssa Famalette – Research Assistant
Vivian Lallo – Research Assistant
LNCD lab members
Research Participants

The entire fourth year bioengineering cohort
BMES and the bioengineering department
Mr. Winston

CNBC Center for the Neural Basis of Cognition
University of Pittsburgh
NIH National Institute of Mental Health
5R01MH067924-17
2T32MH019986-26

Supplemental Slides

Power Analysis

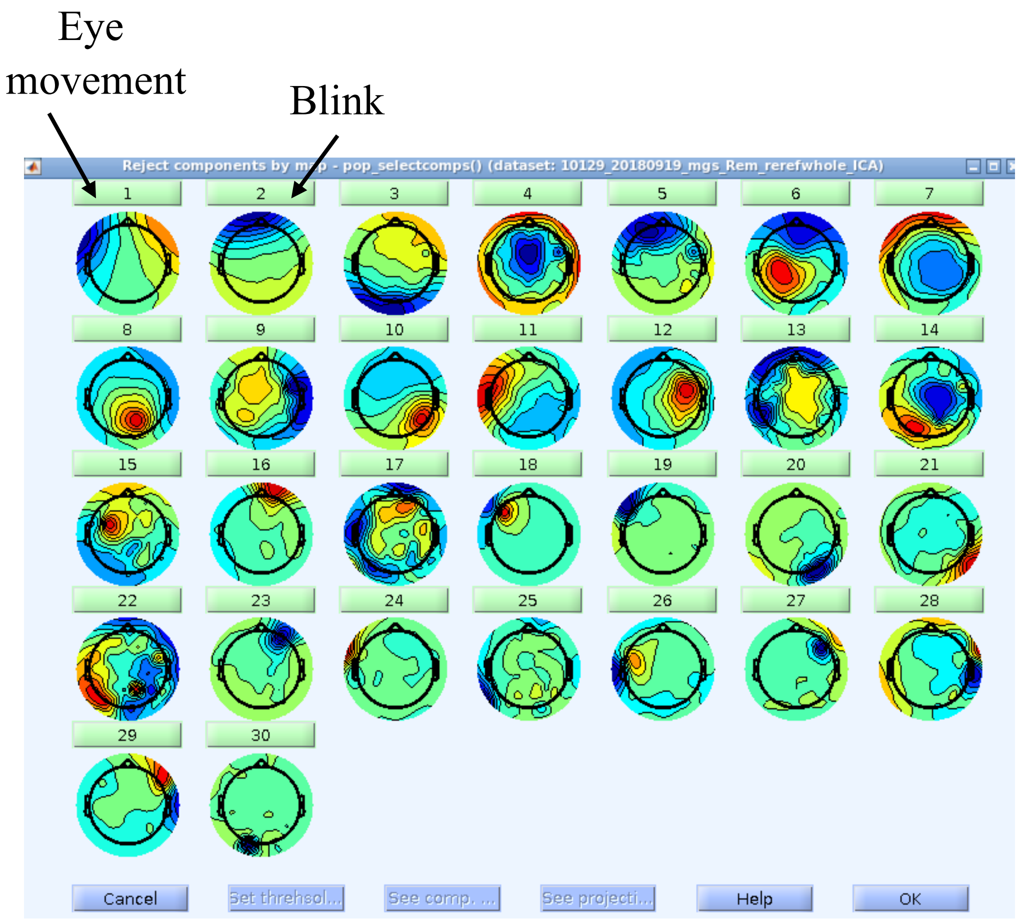
Given an n=164 from our parent grant (R01 MH067924), we will be powered to detect effects for r>0.21 with 80% power. Prior literature investigating EEG gamma power across adolescence have reported r=.31[46] and r=0.29[117]. Our proposed analyses comparing EEG gamma spectral bursts and MRSI GABA/Glu measures has not been done in a developmental context, and thus we based our power analysis on previous literature comparing EEG and physiological measures such as cortical thickness (e.g., r=0.28[118]), suggesting we are likely to sufficiently powered to detect effects in both our EEG and MRSI GABA/Glu measures.

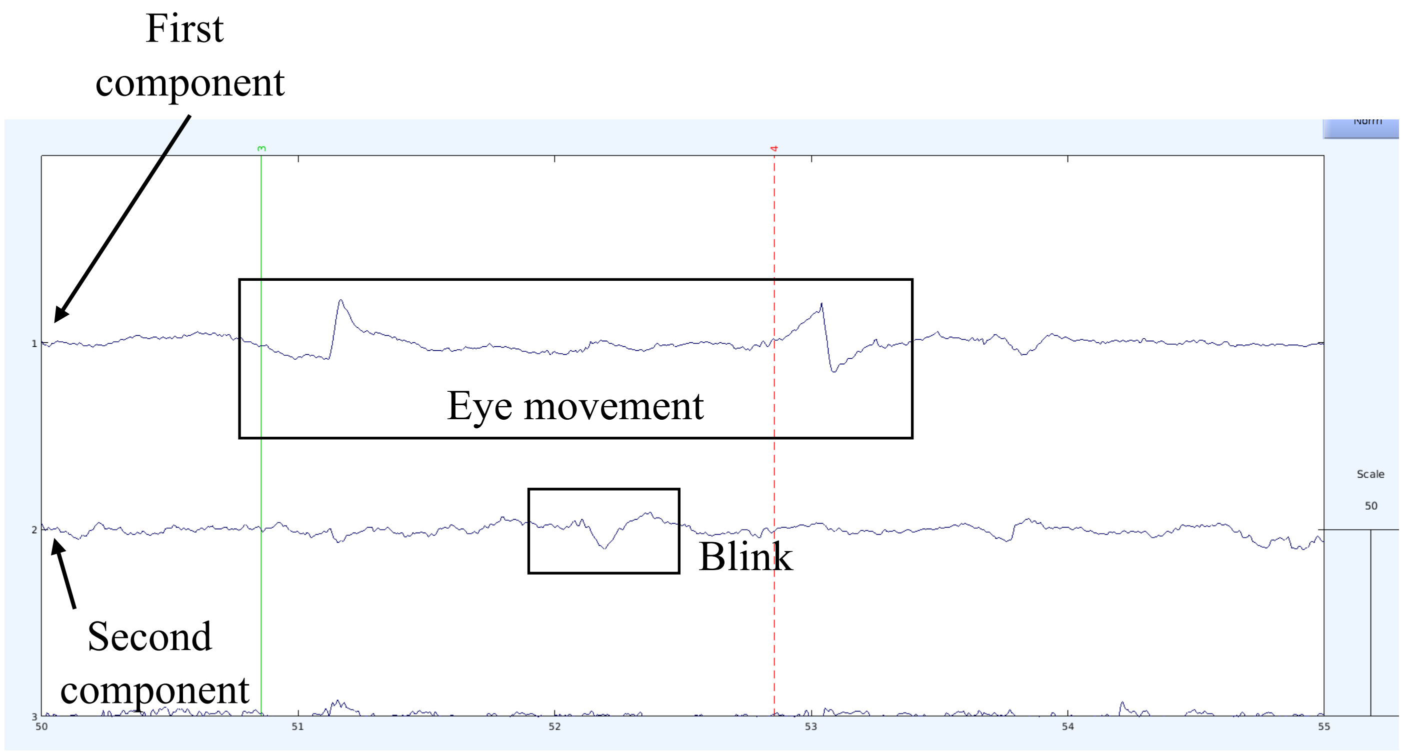
Preliminary sEEG data from 9 subjects collected at rest and averaged over all available electrodes, showed age related decreases in the prevalence (r=0.49) and duration (r=.54) of gamma band events, suggesting such effects can be detected significantly with 80% power given n>29 subjects. To date, n=22 subjects data have been collected, with further collection ongoing, and based on numbers from 2019, we expect approximately 5-10 10-25yo patients without cognitive impairment per year. Thus, achieving an n>29 is feasible within the following year.

MGS Outlier Detection

Preliminary outlier detection was conducted on a trial level basis. Express saccades of less than 100ms, believed to be primarily driven by subcortical systems[39], were excluded. Position error measures greater than 23 degrees from the target were excluded as implausible since they exceeded the width of the screen

Independent Component Analysis (ICA)





Why the DLPFC

- Human postmortem evidence also suggests a peak or plateau in the development of PV expression in human DLPFC[1]
- Dorsolateral PFC (dlPFC) embodying computational mechanisms for monitoring and manipulating items in working memory[2]
    - Functionally specialized to process visuospatial information in working memory
- Early WM requires specialization of brain regions that support visuospatial organization (parietal regions) and maintenance of representations (DLPFC)[3]
    - Adult level WM involves both specialization within these regions

1. Fung et al. (2010). 2. Barbey et al. (2013) 3. Scherf et al. (2006)

Spectral Events Methods

Spectral data were computed for every electrode from the 3000 – 4000ms window of the delay epoch of the task to avoid artifact from preceding eye movements and preparation from an imminent response, and from the 1 second inter-trial fixation epoch. The spectrograms of the data were calculated from 20 to 70 Hz by convolving the signals with a complex Morlet wavelet[37] of the form

$$\omega(t, f_0) = Aexp\left(\left(-\frac{t^2}{2\sigma_t^2}\right)\right)\exp(2i\pi f_0\, t)$$

for each frequency of interest f_0, where $\sigma = m/(2\pi f_0)$. The normalization factor was $A = 1/\sigma_t\sqrt{2\pi}$ and the constant m, defining the compromise between time and frequency resolution, was 7, consistent with previous literature[27]. Time-frequency representations of power (TFR) were calculated as the squared magnitude of the complex wavelet-convolved data. The TFR was normalized to the median power value for each frequency band, derived from all the power values within the identified stimulus windows of the delay and fixation epochs. Normalized TFR values were calculated in factors of median (FOM) for each frequency, separately for each participant/trial.

Defining Events

Gamma events were defined as local maxima in the trial-by-trial TFR matrix for each frequency value at the maxima that fell within the gamma band (35 – 65 Hz) and the power exceeded a cutoff of 6x the median power[27]. This threshold is determined for each individual subject and is epoch specific. Local maxima were found using the Matlab function 'imregionalmax'. Custom software for identifying transient events and event features is written in Matlab and available at

https://github.com/jonescompneurolab/SpectralEvents. Trial average and trial-by-trial variability of each feature were calculated by using the average and standard deviation of each measure (event power, number, and duration) across trials for the delay and fixation epochs separately.

Defining Events

Gamma Event Power

Gamma event power was defined as the normalized TFR value (units of FOM) at the local maximum that defines each event. The trial mean event power was defined as the power of all events averaged in the 3000 – 4000 ms window of the delay epoch and the 0 – 1000 ms window of the fixation epoch.

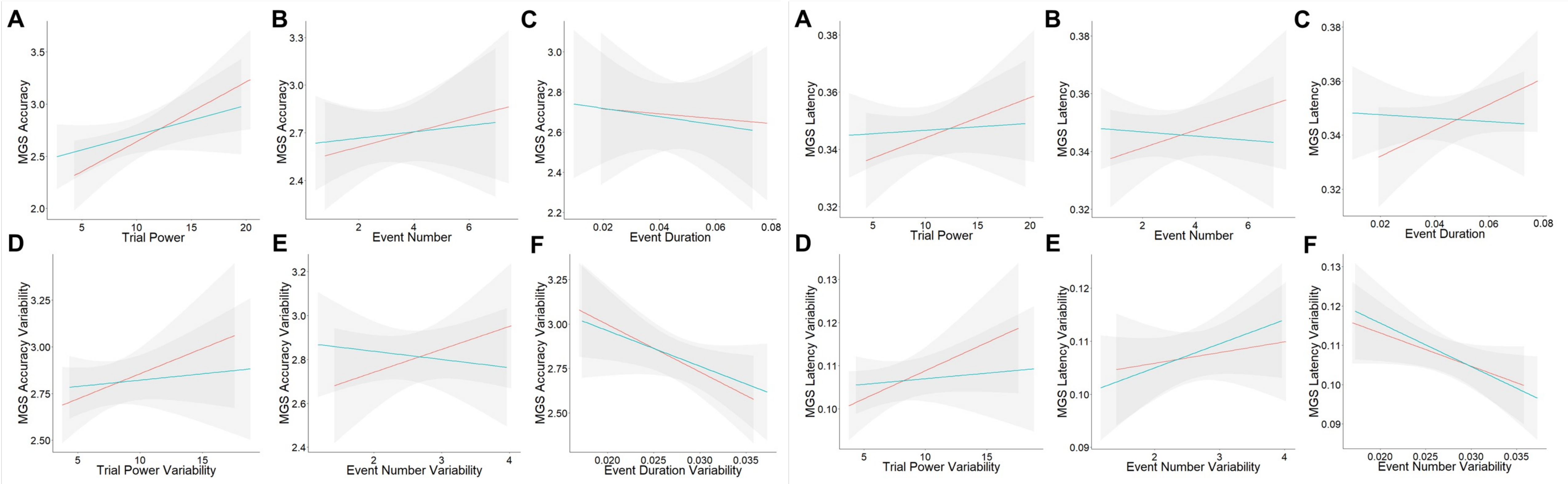
Gamma Event Number

Gamma event number was calculated as the number of gamma events in the 3000 – 4000 ms window of the delay epoch and the 0 – 1000 ms window of the fixation epoch.

Gamma Event Duration and Frequency Span

Event duration and frequency span are calculated as full- width- half- maximum (FWHM) from the event maxima in the time and frequency domain, respectively.

All spectral measures (power, number of events, duration of events, and variability of each) were averaged across electrodes F3, F5, and F7 to create average spectral event measures for the left DLPFC, and F4, F6, and F8 for the right DLPFC based on the region of interest analysis performed on the total TFR power of each epoch window.



L DLPFC
R DLPFC

Aim 1: Preliminary Results

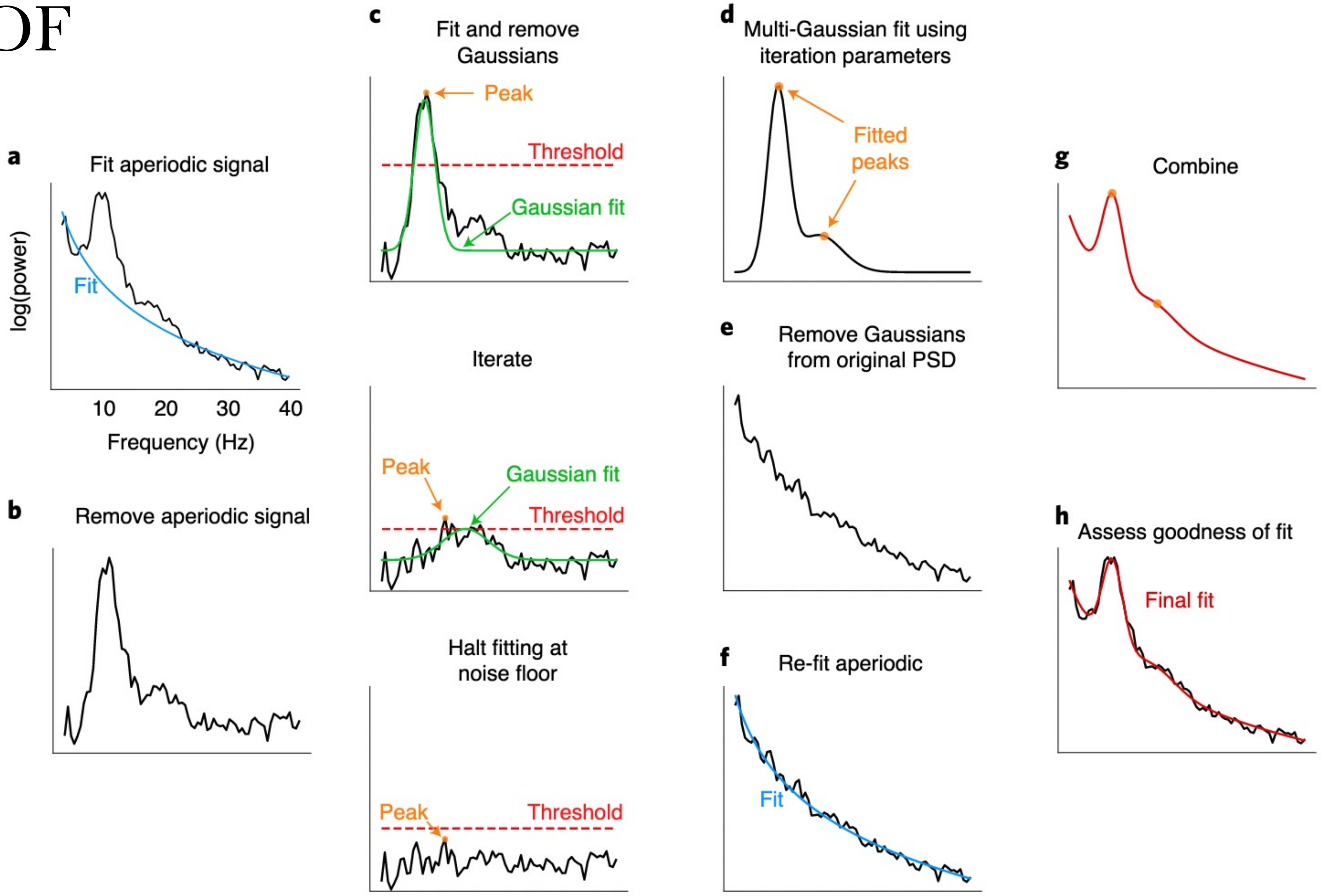
MRS

- While MRS is not sensitive enough to pick up on specific changes in PV-positive neurons, it instead reflects a com posite view of many aspects of GABA signaling, providing a more generalized measure of the overall tone of GABAergic inhibition (Perica et al, 2022)
- In contrast, the lack of age effects for GABA levels in the DLPFC and MPFC are in line with a recent meta-analysis of MRS data showing GABA stability through adolescence (Porges et al., 2021).

MRI Spectroscopy

- Siemens 7T scanner - **MP2RAGE** sequence for parcellation and alignment
- MRSI of GABA and glutamate acquired using a **J-refocused spectroscopic imaging sequence**[114] to minimize the impact of momentary interactions between separate molecules on chemical shifts.
- An oblique axial slice, with **0.9 x 0.9 x 1.0 cm** voxels was acquired and positioned to ensure that the DLPFC (Brodmann Area 9) was present.
- NT levels was achieved by fitting the MRSI data using **LCModel**[115]
    - Metabolite **ratios to creatine** (Cr) (Glu/Cr or GABA/Cr),
        - **Allowing for shorter acquisition time**
        - Control for **inter-subject variability** due to factors such as volume of cerebrospinal fluid[106].
        - **Cr was selected due to its strong signal and reliable chemical shift.**
    - Regions of interest (ROIs) were mapped into each subject's native space using an automated nonlinear registration using **FSL's FNIRT.**
    - Regions were registered back to standard space and positioning was confirmed with the Eickhoff-Zielles maximum probability map of the **Talairach-Tournoux atlas**[116].
    - Data quality was visually inspected and excluded for bad model fits due to artifact, lipid contamination, and/or baseline distortion. Further data preprocessing and **quality control was performed based on the three major metabolic peaks** Furthermore, GABA/Cr and Glu/Cr data was excluded if the **CRLB of GABA or glutamate was greater than 20.** On the subject level, individual ROIs were removed for poor data quality, while on the group level analyses, outlier detection was performed, excluding subjects more **than +/-2 SDs away from the mean.**

FOOOF


a
Fit aperiodic signal
log(power)
Fit
10
20
30
40
Frequency (Hz)
b
Remove aperiodic signal
c
Fit and remove Gaussians
Peak
Threshold
Gaussian fit
Iterate
Peak
Gaussian fit
Threshold
Halt fitting at noise floor
Peak
Threshold
d
Multi-Gaussian fit using iteration parameters
Fitted peaks
e
Remove Gaussians from original PSD
f
Re-fit aperiodic
Fit
g
Combine
h
Assess goodness of fit
Final fit

FOOOF Periodic Model Fitting

Mathematical Description of the Periodic Component

To fit this periodic activity - the regions of power over above the aperiodic component, or 'peaks' - the model uses Gaussians. As we've seen, there can be multiple peaks in the model.

Each Gaussian, n, referred to as $G(F)n$, is of the form:

$$G(F)_n = a * exp(\frac{-(F-c)^2}{2 * w^2})$$

This describes each peak in terms of parameters a, c and w, where:

- a is the height of the peak, over and above the aperiodic component
- c is the center frequency of the peak
- w is the width of the peak
- F is the array of frequency values

FOOOF Aperiodic Model Fitting

To fit the aperiodic component, we will use the function L:

$$L(F) = b - \log(k + F^{\chi})$$

Note that this function is fit on the semi-log power spectrum, meaning linear frequencies and log_{10} power values.

In this formulation, the parameters b, k, and χ define the aperiodic component, as:

- b is the broadband 'offset'
- k is the 'knee'
- χ is the 'exponent' of the aperiodic fit
- F is the array of frequency values

Note that fitting the knee parameter is optional. If used, the knee parameter defines a 'bend' in the aperiodic *1/f* like component of the data. If not used, the 'knee' parameter is set to zero.

This function form is technically described as a Lorentzian function. We use the option of adding a knee parameter, since even though neural data is often discussed in terms of having *1/f* activity, there is often not a single *1/f* characteristic, especially across broader frequency ranges. Therefore, using this function form allows for modeling bends in the power spectrum of the aperiodic component, if and when they occur.

Note that if we were to want the equivalent function in linear power, using AP to indicate the aperiodic component in linear spacing, it would be:

$$AP(F) = 10^{b} * \frac{1}{(k + F^{\chi})}$$

LFP feature extraction.

We measured oscillatory power in the LFP signal using Morlet wavelets (wave number 4) at 50 log-spaced frequencies between 2 and 150 Hz (2 10 0.0383x for x {0 . . . 49}). Because oscillatory power at a given frequency is 2 distributed (Percival and Walden, 1993; Henrie and Shapley, 2005), we log-transformed the wavelet-calculated powers to make the distributions more normal. To account for interelectrode impedance differences, we normalized the powers recorded at each electrode such that the mean power spectrum was centered at 0 with an SD of 1

LFP Power vs Firing Rate

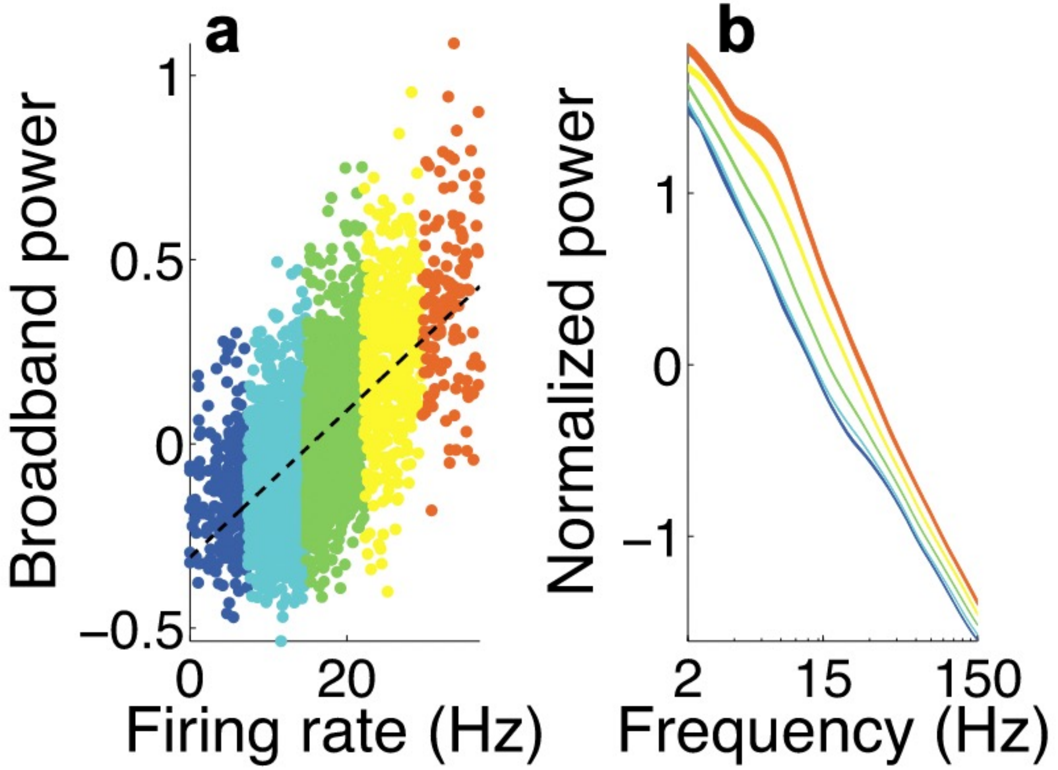


Figure 2. A representative neuron exhibiting a positive correlation between firing rate and broadband LFP power. ***a***, Broadband power and firing rate for the neuron analyzed in Figure 1. Each 500 ms epoch of the recording session is represented by one colored dot. The color of each dot represents its relative firing rate. Warm colors depict epochs with high firing rates, and cool colors indicate epochs with low firing rates. The dashed black line shows an ordinary least-squares regression to these data. ***b***, Average LFP power spectra for epochs with different firing rates. The same color scheme is used in both panels. As firing rate increases, the power spectrum exhibits a positive shift at all observed frequencies. The thickness of each line represents ±1 SEM.

Coverage
bilateral parietal lobes, also some coverage in the temporal lobe and frontal lobe on the left and right side
bilateral temporal lobes and right frontal operculum
left superior temporal gyrus
left temporal lobe including the amygdala, hippocampus, entorhinal cortex, temporal operculum, and temporal neocortex and right frontal lobe; also left frontal operculum, left inferior frontal gyrus, and middle frontal gyrus.
right temporal structures including the supratemporal plane, amygdala, hippocampus, entorhinal cortex, and the inferior temporal lobe
right and left occipital and parietal regions as well as the right temporal region
right temporal lobe, right temporal and frontal operculum, right frontal lobe
left temporal lobe including the amygdala, hippocampus, entorhinal cortex, supratemporal plane, frontal operculum, and insula
right amygdala, hippocampus, frontal and temporal operculum, and entorhinal cortex
frontal and parietal lobes
Removed From S
insulo-opercular, frontal, and parietal regions, and the entire right cingulate gyrus
each temporal lobe including the supratemporal plane, nebula, hippocampus, temporal pole, infrarenal cortex, and occipital temporal sulci
right temporal lobe including the amygdala, hippocampus, temporal operculum, inferior temporal gyrus, and entorhinal cortex; also included coverage of the right SMA and the right cingulate
L orbital frontal region, frontal operculum, temporal operculum, amygdala, hippocampus, entorhinal cortex, and temporal neocortex
R frontotemporal region including cingulate, hippocampus, and amygdala
L frontoparietal cortex and residual amygdalar tissue (previous amygdalohippocampectomy)
L superior temporal gyrus and mid-temporal gyrus
BL frontoparietal regions, perisylvian cortex including the insula
L frontal lobe
R frontal lobe, parietal lobe, motor cortex, somatosensory cortex, insular and cingulate regions
R temporal occipital region including periventricular grey matter
R insula, temporal lobe, and parietal cortex
BL frontal & parietal cortex, BL insula, L parieto-occipital & temporal cortex
BL frontoparietal regions, perisylvian cortex including the insula
R insulo-opercular region, BL frontal cortex
L posterior parietal, posterior temporal, occipital cortex
R frontal and temporal cortex
BL frontal and temporal lobes

Limitations

EEG presents a major limitation on the basis of extracranially recorded signals concerns the propagation of volume conduction between electrodes

Associations between EEG and working memory (Aim 1) may not be present, as working memory involves a wide circuitry of neuronal activity, and is more commonly related to EEG activity in terms of working memory load

ASSR task has advantages in detecting SNR and gamma band specific disturbances, it does not directly link oscillatory activity to a cognitive process

MRSI has its own limitations; even at 7T field strength, measuring metabolites such as GABA present difficulty in maximizing magnetic field homogeneity and require relatively longer acquisition times to acquire low concentration metabolities

sEEG has limitations in terms of the inconsistent coverage across patients, as electrode placement locations is determined by seizure activity however given that we are measuring neural activity directly. Furthermore, sEEG recruitment is limited to patients seeking epilepsy treatment