# Prefrontal Excitation/ Inhibition Balance Supports Adolescent Enhancements in Circuit Signal to Noise Ratio

Shane D. McKeon[1,2], Maria I. Perica[2,3], Finnegan J. Calabro[1,2,4], Will Foran[4], Hoby Hetherington[5,6], Chan-Hong Moon[7], Beatriz Luna[2,4]

1. Department of Bioengineering, University of Pittsburgh, PA, USA. 2. The Center for the Neural Basis of Cognition, University of Pittsburgh, PA, USA. 3. Department of Psychology, University of Pittsburgh, PA, USA. 4. Department of Psychiatry, University of Pittsburgh, PA, USA. 5. Resonance Research Incorporated, Billerica, MA, USA. 6. Department of Radiology, University of Missouri, Columbia, MO, USA . 7. Department of Radiology, University of Pittsburgh, PA, USA

## BACKGROUND

Animal[1-2] and human postmortem[3-4] studies provide evidence that processes underlying excitatory/inhibitory (E/I) balance in prefrontal cortex (PFC) increase through adolescence into adulthood reflecting unique neural plasticity believed to support the maturation of executive function into adulthood.

Our previous work has found increases in MRSI derived measures of glutamatergic excitatory/GABAergic inhibitory (E/I) balance[5-6] through adolescence that is in accord with EEG evidence of developmental decreases in the aperiodic exponent during resting state[5].

Developmental attainment of E/I balance in PFC should lead to fine-tuning of cortical circuitry resulting in enhanced neural population synchronization suppressing large asynchronous spontaneous activity leading to increases in signal-to-noise ratio (SNR) that may underlie improvements and stabilization of executive function into adulthood[7].

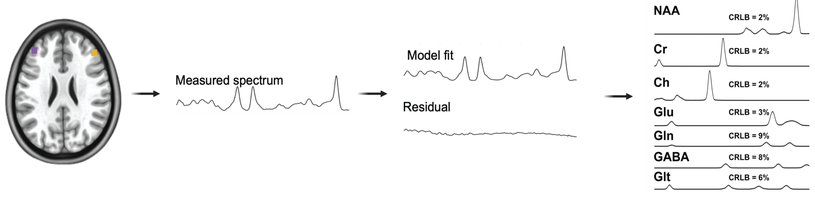
Here, we present findings from the **auditory steady state response (ASSR) task,** including a 40hz gamma-band inducing stimuli[8,9] that reflects the interplay between GABAergic inhibitory neurons and excitatory pyramidal neurons[10-12], in the same participants with MRSI glutamate/GABA data and working memory performance.

***We hypothesized a developmental transition through adolescence from predominantly spontaneous to evoked activity in PFC indicating enhancements in SNR supporting improvements in executive function.***

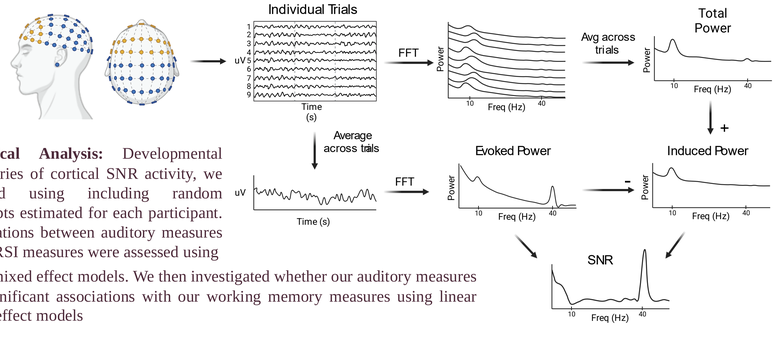
## METHODS

**Participants:** 164 10-32yos completed an EEG and MRS study, up to 3 timepoints, for a total of 286 sessions.

**MRSI:** 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. Glu/GABA balance was determined by taking the absolute value residual of the linear model of the association between Glu/Cr and GABA/Cr.



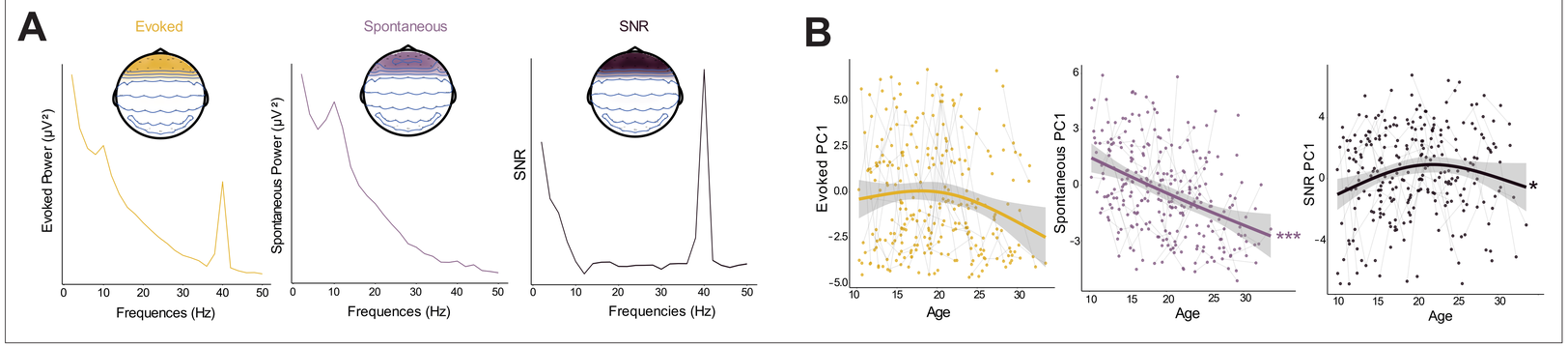

**EEG:** Auditory steady state task using a 20, 30, and 40 HZ stimuli. PCA was done on frontal electrodes, given previous ASSR response observed in the frontal cortex[13]. Power spectra were averaged across trials to compute total power. Evoked power was then derived by averaging trial time courses and taking the FFT. Spontaneous power was derived by subtracting the evoked power from the total power. SNR was calculated as the ratio of evoked power to spontaneous power.



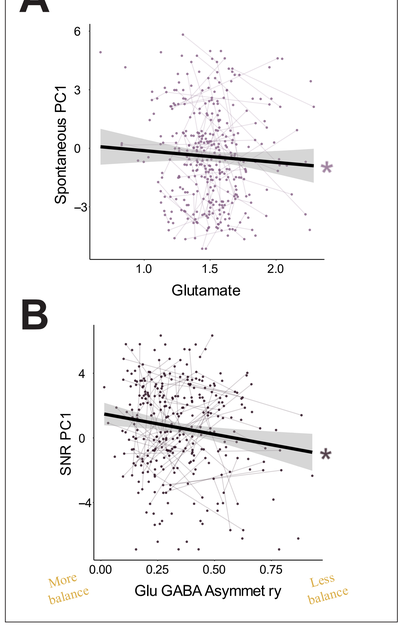

**Statistical Analysis:** Developmental trajectories of cortical SNR activity, we assessed using including random intercepts estimated for each participant. Associations between auditory measures and MRSI measures were assessed using linear mixed effect models. We then investigated whether our auditory measures had significant associations with our working memory measures using linear mixed effect models

## RESULTS

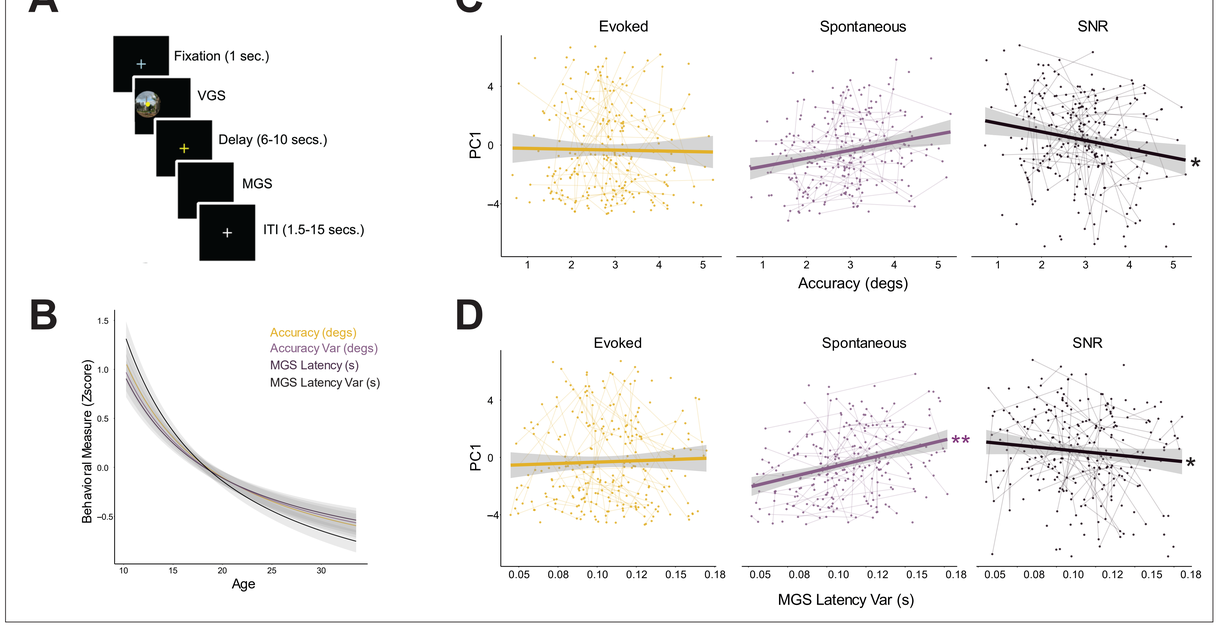
### 1. PFC cortical SNR increases across adolescence driven by significant decreases in spontaneous activity




### 2. Increased E/I balance is associated with increased PFC cortical SNR




### 3. Increased cortical SNR is associated with improved working memory performance




## CONCLUSIONS

These results provide *in vivo* human evidence that **PFC SNR increases as the E/I circuitry becomes balanced** supporting cognitive development. These improvements in SNR appear to be driven by developmental decreases in glutamatergic excitatory/spontaneous function, that may reflect known synaptic pruning of excitatory synapses. Together, these results add to our model of adolescent brain development highlighting neural mechanisms that underlie the transition from adolescent exploratory/spontaneous function to stabilization in adulthood. Identifying these neural mechanisms of normative PFC plasticity can inform atypical trajectories such as in mental illnesses that emerge at this time.

## ACKNOWLEDGEMENTS

We thank the University of Pittsburgh Clinical and Translational Science Institute (CTSI) for support in recruiting participants, as well as their support by the National Institutes of Health through grant number UL1TR001857. We thank Matthew Missar, Laurie Thompson, Alyssa Famalette, Vivian Lallo, Piya Verma, and Angela Martinez for their work involving our data collection. This work was supported by MH067924 from the National Institute of Mental Health, T32 Training Grant Number T32MH019986 from the National Institute of Mental Health, F31 Grant Number 1F31MH132246, the Staunton Farm Foundation, and support from the Department of Bioengineering, University of Pittsburgh.

**Contact: sdm63@pitt.edu**

## REFERENCES

**1.** Chattopadhyaya B., et al. Experience and activity-dependent maturation of perisomatic GABAergic innervation in primary visual cortex during a postnatal critical period. *J. Neurosci.* 2004. **2.** Micheva K.D., Beaulieu C. Development and plasticity of the inhibitory neocortical circuitry with an emphasis on the rodent barrel field cortex: a review. *Can. J. Physiol. Pharmacol.* 1997. **3.** Mauney S.A., et al. Developmental Pattern of Perineuronal Nets in the Human Prefrontal Cortex and Their Deficit in Schizophrenia. *Biol. Psychiatry.* 2013. **4.** Fung S.J., et al. Expression of Interneuron Markers in the Dorsolateral Prefrontal Cortex of the Developing Human and in Schizophrenia. *AJP.* 2010. **5.** McKeon SD, Perica MI, Parr AC, et al. Aperiodic EEG and 7T MRSI evidence for maturation of E/I balance supporting the development of working memory through adolescence. *Dev Cogn Neurosci.* 2024. **6.** Perica M.I., et al. Development of frontal GABA and glutamate supports excitation/inhibition balance from adolescence into adulthood. *Prog. Neurobiol.* 2022. **7.** Tervo-Clemmens, B., Calabro, F.J., Parr, A.C. *et al.* A canonical trajectory of executive function maturation from adolescence to adulthood. *Nat Commun.* 2023. **8.** Galambos, R., Makeig, S. & Talmachoff, P. J. A 40-Hz auditory potential recorded from the human scalp. *PNAS* (1981). **9.** Picton, T. W., John, M. S., Dimitrijevic, A. & Purcell, D. Human auditory steady-state responses: Respuestas auditivas de estado estable en humanos. *Int J of Audiology* (2003). **10.** Vohs, J. L. *et al.* GABAergic modulation of the 40 Hz auditory steady-state response in a rat model of schizophrenia. *Int J of Neuropsychopharmacol* (2010). **11.** Sivarao, D. V. *et al.* 40 Hz Auditory Steady-State Response Is a Pharmacodynamic Biomarker for Cortical NMDA Receptors. *Neuropsychopharmacol* (2016). **12.** Sullivan, E. M., Timi, P., Hong, L. E. & O'Donnell, P. Effects of NMDA and GABA-A Receptor Antagonism on Auditory Steady-State Synchronization in Awake Behaving Rats. *Int J of Neuropsychopharmacol* (2015). **13.** Tada M, Kirihara K, Ishishita Y, et al. Global and Parallel Cortical Processing Based on Auditory Gamma Oscillatory Responses in Humans. *Cereb Cortex.* 2021