Reliability of cortical signal processing is driven by glutamate maturation, and supports working memory development

Shane McKeon[1], Finnegan Calabro[1,2], Maria Perica[3], Beatriz Luna[2]

[1]Department of Bioengineering, [2]Department of Psychiatry, [3]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

BACKGROUND

Postmortem animal & human models indicate changes in excitatory glutamatergic (Glu)[1] and inhibitory GABAergic[2] processes in prefrontal cortex through adolescence including our recent *in vivo* MRSI evidence of changes in Glu/GABA balance[3] suggestive of critical period plasticity. We have hypothesized that E/I balance may enhance cortical signal to noise ratio (SNR) by suppressing spontaneous, asynchronous activity and increasing evoked, synchronous activity, supporting enhancements in cognitive control[4]. Here we test the hypothesis that developmental increases in dorsolateral prefrontal E/I balance will be accompanied by enhanced SNR and improved working memory.

METHODS

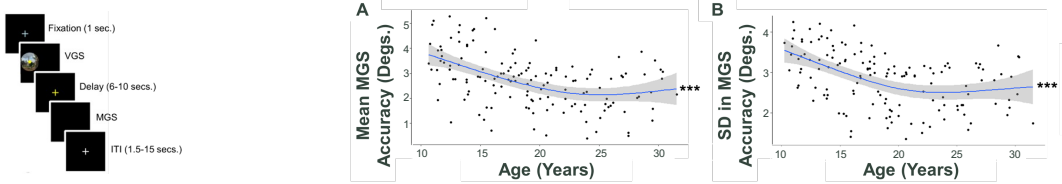
148 10-30yos (77 females) performed an EEG study during auditory steady state and a memory guided saccade task as well as a Magnetic Resonance Spectroscopic Imaging scan at 7T with multiple voxels across prefrontal cortex.

Evoked activity was derived from the spectral decomposition of the auditory SS task in the 50-200ms following onset of an auditory cue. **Spontaneous activity** was defined as the variance of EEG activity across the entire task epoch, averaged across trials. **SNR** was defined as the difference between evoked and spontaneous activity. **E/I balance** was defined as the absolute difference between GABA and Glu levels.

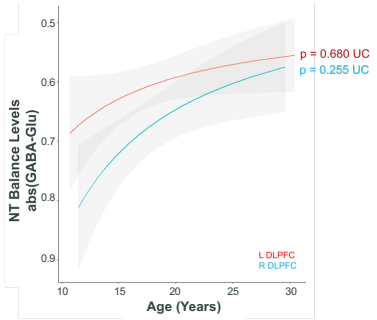
Linear mixed-effects models were used to compare SNR EEG and MRSI measures of GABA & Glu in the left and right DLPFC and MGS performance. Bonferroni was used to correct for multiple comparisons.

RESULTS

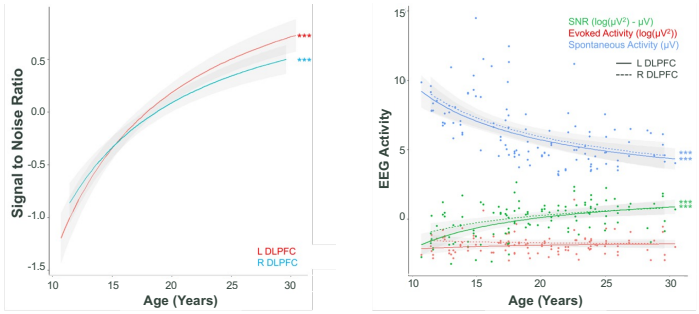
Working memory accuracy improves into adulthood as variability in accuracy decreases

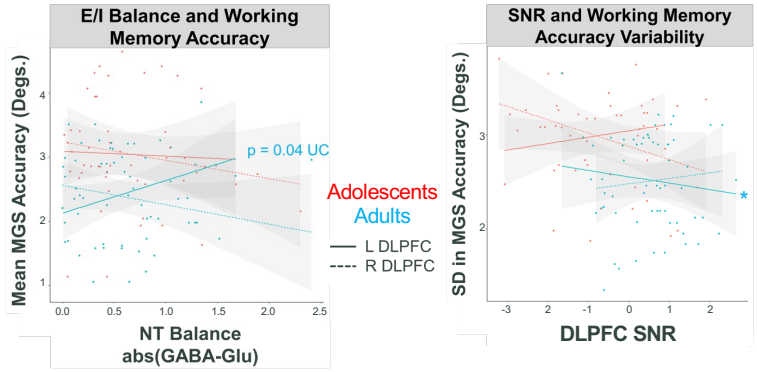


GABA/Glu balance increases with age across PFC regions.



SNR increases with age across the DLPFC, driven by decreases in spontaneous activity.





In adulthood, increased E/I balance shows a trend for association with better working memory *accuracy*.

In adulthood, greater SNR in the Left DLPFC is associated with decreases in *variability* of working memory accuracy.

CONCLUSION

These findings suggest that age-related increases in E/I balance into adulthood may underlie enhanced SNR supporting developmental improvements in working memory and reflecting critical period plasticity.

Working memory accuracy and variability were uniquely associated with left DLPFC enhancements in SNR and E/I balance in adulthood which may reflect how in the mature system L DLPFC has been associated with unique contributions to temporal processes underlying maintenance[5], which increased SNR may enhance.

REFERENCES & ACKNOWLEDGEMENTS

1. Petanjek,Z. et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc. Natl. Acad. Sci.* 2011.
2. Kilb, W. Development of the GABAergic System from Birth to Adolescence. *The Neuroscientist* . 2012
3. Perica, Maria. et al. Changes in prefrontal GABA and glutamate through adolescence supports excitation/inhibition balance. *BioRxiv*. 2022.
4. Larsen, Bart. Luna, Beatriz. Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neurosci Biobehav Rev*. 2018.
5. Barbey, Aron. et al. Dorsolateral prefrontal contributions to human working memory. *Cortex*. 2013.

We thank the University of Pittsburgh Clinical and Translational Science Institute (CTSI) for help in recruiting participants. We thank Matthew Missar and Alyssa Famalette for their work involving our data collection. This work was supported by Grant Number 5R01MH067924-17 from the National Institutions of Mental Health and support from the Department of Bioengineering, University of Pittsburgh.