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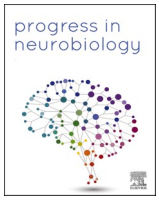

Prefrontal excitation/inhibition balance supports adolescent enhancements in circuit signal to noise ratio

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ABSTRACT

The development and refinement of neuronal circuitry allow for stabilized and efficient neural recruitment, supporting adult-like behavioral performance. During adolescence, the maturation of PFC is proposed to be a critical period (CP) for executive function, driven by a break in balance between glutamatergic excitation and GABAergic inhibition (E/I) neurotransmission. During CPs, cortical circuitry fine-tunes to improve information processing and reliable responses to stimuli, shifting from spontaneous to evoked activity, enhancing the SNR, and promoting neural synchronization. Harnessing 7 T MR spectroscopy and EEG in a longitudinal cohort (N = 164, ages 10–32 years, 283 neuroimaging sessions), we outline associations between age-related changes in glutamate and GABA neurotransmitters and EEG measures of cortical SNR. We find developmental decreases in spontaneous activity and increases in cortical SNR during our auditory steady state task using 40 Hz stimuli. Decreases in spontaneous activity were associated with glutamate levels in DLPFC, while increases in cortical SNR were associated with more balanced Glu and GABA levels. These changes were associated with improvements in working memory performance. This study provides evidence of CP plasticity in the human PFC during adolescence, leading to stabilized circuitry that allows for the optimal recruitment and integration of multisensory input, resulting in improved executive function.

1. Introduction

Adolescence is a time of cognitive development that stabilizes in adulthood (Tervo-Clemmens et al., 2023), where the prefrontal cortex (PFC) is essential for cognitive processes and undergoes significant maturation, reflecting unique plasticity (Larsen and Luna, 2018; Fuster, 2002). Postmortem studies in both animal and human models provide evidence of neurotransmitter changes involving glutamate and Gamma-Aminobutyric Acid (GABA) (Kilb, 2012), indicating a shift in E/I balance similar to critical period (CP) plasticity observed in sensory cortices earlier in development (Larsen and Luna, 2018). This shift includes alterations in parvalbumin (PV)-positive interneurons, a sub-type of inhibitory GABAergic interneuron known for its highly interconnected and fast-spiking activity, which enables them to synchronize and generate gamma oscillations observable via electroencephalography (EEG). Moreover, PV interneurons modulate their firing rates in response to excitatory input, serving as a crucial local gain control (Scholl et al., 2015) and contributing to the regulation of the E/I balance (Larsen and Luna, 2018). The fine-tuning of cortical circuitry during CPs enhances the circuit's ability to produce consistent, reliable, and prompt responses to stimuli (Larsen and Luna, 2018). This transition involves a shift from predominantly spontaneous to evoked activity, which enhances the cortical SNR, facilitates neural population synchronization, and suppresses large asynchronous spontaneous activity (Hensch, 2005; Toyoizumi et al., 2013a; Hensch and Fagiolini, 2005). This activity is thought to support executive functioning by stabilizing

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task-evoked activity, thus reducing performance variability on cognitive tasks for which accuracy and latency have been consistently shown to continue to improve into the twenties (Tervo-Clemmens et al., 2023; Montez et al., 2017; Simmonds et al., 2017; Alloway et al., 2006; Luna et al., 2004; Geier et al., 2009; McKeon et al., 2023a). However, while evoked and spontaneous oscillations have been assessed, this shift in cortical SNR has not been studied *in vivo* in humans. Thus, this study aims to investigate cortical SNR using EEG and its associations with the E/I balance via MRSI measures of GABA and Glu, as a marker for CP plasticity during adolescence.

In early stages of neuronal development, spontaneous activity is prevalent and helps to shape neural circuit excitatory and inhibitory properties. For example, the influx of excitatory activity when light first hits the eye in the visual system helps to initiate a CP of circuit refinement (Hensch, 2005; Wiesel and Hubel, 1963). The number of synapses in PFC are greater in adolescence than adulthood, which will be subsequently pruned (Kolb and Gibb, 2011; Huttenlocher, 1979), resulting in increased excitatory over inhibitory activity. This hyperexcitable circuit function is thought to be important for the refinement of neuronal projections and neural wiring (Mazzoni et al., 2007). In response to the relative increase of excitatory function, the GABAergic inhibitory system undergoes significant maturation (Wu and Sun, 2015; Li et al., 2020) modulating neural activity by braking excitatory signaling. Thus, spontaneous activity during development may modulate excitatory and inhibitory synaptic efficacy (Gonzalez-Islas and Wenner, 2006), thereby influencing the E/I balance throughout development and sculpting adult-like neuronal networks (Haider et al., 2006). Animal models suggest that PFC GABAergic inhibitory circuitry undergoes significant alterations, including an increase in prefrontal PV+ interneurons during adolescence in the rat (Caballero et al., 2014a) and non-human primate (Hoftman et al., 2015). Furthermore, non-human primate and human postmortem studies have shown increases in PV interneurons (Fung et al., 2010) and GABAA receptor α1 subunit expression (Duncan et al., 2010). Primarily expressed on PV interneurons, GABAA receptor α1 subunits support fast synaptic inhibition (Bosman et al., 2002) and synaptic plasticity (Katagiri et al., 2007). In conjunction, excitatory pyramidal PFC neurons undergo significant pruning across the adolescent period (Selemon, 2013). These findings provide evidence suggesting CP plasticity in PFC akin to CPs observed in sensory systems, such as the development of PV+ interneuron circuitry and excitatory circuit maturation (Katz and Shatz, 1996; Toyoizumi et al., 2013b), which facilitate experience-driven CP plasticity (Katagiri et al., 2007; Fagiolini et al., 2004).

The interplay between PV+ interneurons, in particular basket cells, that innervate on the soma of pyramidal neurons, generate gamma oscillations (Ferguson and Gao, 2018; Cho et al., 2015a; Buzsáki and Wang, 2012). The regulation of which occurs at both the single neuron level, regulated by the number of excitatory and inhibitory synapses on cortical pyramidal neurons, and the large-scale circuitry level, where numerous homeostatic and developmental processes help maintain the E/I balance across long timescales (Sohal and Rubenstein, 2019). These two levels, while independent, work in conjunction as stimulated neurons in one population propagate other neurons across multiple cortical layers, until sufficient inhibition is reached to maintain balance (Adesnik and Scanziani, 2010; Yizhar et al., 2011). Coupled together, both levels contribute to the appropriate modulation of the inhibition excitation activity needed to generate gamma oscillations (Lally et al., 2014), allow for efficient information transmission and gating (Salinas and Sejnowski, 2001), network computation (Mariño et al., 2005), and higher order cognitive functions, such as working memory (Lim and Goldman, 2013).

Developmental changes in spontaneous and evoked activity have been studied via the auditory steady state response (ASSR), which uses a train of auditory clicks delivered at high frequencies, typically at 20, 30 or 40 Hz, that have been demonstrated to elicit robust oscillations that can be noninvasively measured through EEG. This phenomenon, known as entrainment, is driven by a phase adjustment of the underlying oscillations to match the stimulus frequency and an increase in amplitude at the neural population level as more neurons become aligned to the stimuli (Thut et al., 2011; Sugiyama et al., 2023). This is thought to be propelled by a circuit's preferred resonance frequency at which the auditory stimuli induces the most entrainment (Galambos et al., 1981; Başar et al., 1987), and is referred to as the evoked activity. In contrast, spontaneous power of gamma oscillations is non-stimulus locked, allowing the parsing of task-locked from non-locked activity to infer relative levels of spontaneous and evoked activity and, consequently, cortical SNR. Previous studies have demonstrated that the greatest and most reliable evoked response is yielded by a 40 Hz stimuli (Galambos et al., 1981; Picton et al., 2003), and has been historically used to assess the ability to generate gamma-band (30–80 Hz) activity (Cho et al., 2015a; Tada et al., 2020; Sugiyama et al., 2021; Hirano et al., 2015; Mathalon and Sohal, 2015; Uhlhaas and Singer, 2010; Thuné et al., 2016; O'Donnell et al., 2013; Oda et al., 2012; Parker et al., 2019; Spencer et al., 2008; Light et al., 2006; Tada et al., 2016; Parciauskaite et al., 2019; Tada et al., 2023; Parciauskaite et al., 2021). Furthermore, animal models have shown the 40 Hz ASSR is maintained by N-methyl-D-aspartate (NMDA) receptors on pyramidal neurons and GABA systems (Vohs et al., 2010; Sivarao et al., 2016; Sullivan et al., 2015), demonstrated via pharmacological studies using NMDA antagonist ketamine (Saunders et al., 2012; Plourde et al., 1997) and the GABAA agonist muscimol (Vohs et al., 2010), where power in the 40 Hz ASSR increases.

While the ASSR primarily targets auditory-responsive regions, including those in the temporal and parietal lobes (Farahani et al., 2021; Herdman et al., 2003; Popescu et al., 2008; Kuriki et al., 2013), it has also been observed in PFC regions when presented with a 40 Hz stimulation (Farahani et al., 2021, 2017; Koshiyama et al., 2021a; Mancini et al., 2022; Tada et al., 2021; Wang et al., 2020; Manting et al., 2020; Shahriari et al., 2016; Koshiyama et al., 2020), both in studies of schizophrenia (Thuné et al., 2016; Light et al., 2006; Farahani et al., 2021; Brenner et al., 2003; Hamm et al., 2015; Koshiyama et al., 2018) and in studies of healthy controls (Koshiyama et al., 2021a). This distribution indicates that ASSR generation engages both auditory cortex and frontal lobe activity, with signals reaching frontal electrodes through volume conduction rather than originating exclusively from the frontal cortex. Both human and animal models have shown that ASSR generation comes from the interaction between GABAergic interneurons and glutamatergic neurons (Cardin et al., 2009; Sohal et al., 2009), both of which are prominent in the prefrontal cortex (Tremblay et al., 2016). Previous studies interrogating the underlying source of the ASSR have looked at the tuning characteristics of individual electrodes and found different characteristics between parietal and frontal cortex, suggesting the auditory response is occurring in parallel in different pathways (Tada et al., 2021).

Gamma oscillations, specifically around 40 Hz, are critical for executive functions, such as working memory and attention (McKeon et al., 2023a; Honkanen et al., 2015; Yamamoto et al., 2014; Barr et al., 2014; Lundqvist et al., 2016), which rely on the synchronization of distributed neural networks. The 40 Hz stimulus used in ASSR paradigms entrains gamma activity, which is involved in both local and network-level mechanisms, which supports cognition (McKeon et al., 2023a; Parciauskaite et al., 2021; Barr et al., 2014; Lundqvist et al., 2016). The ASSR measurable at frontal electrodes thus reflects the combined activity of multiple underlying regions, including orbitofrontal, bilateral superior/middle/inferior temporal, bilateral middle frontal, and posterior cingulate gyri (Koshiyama et al., 2021a). Dipole analyses also support this, identifying clusters of ASSR sources beyond the auditory cortex, extending into the medial and lateral frontal areas (Farahani et al., 2017). Furthermore, recent human (Farahani et al., 2021; Manting et al., 2020) and animal (Shahriari et al., 2016; Toader et al., 2020) models have shown a significant involvement of PFC in

gamma- range ASSR generation. One explanation of this broader distribution is that auditory entrainment may require top-down attentional modulation that may be maintained by the frontoparietal attention network (Ross et al., 2010; Bouwer, 2022). Importantly, the ASSR at the frontal midline has been previously linked to cognitive functions, such as working memory (Light et al., 2006; Tada et al., 2016; Koshiyama et al., 2021b), suggesting that while the signal may be originating from the auditory cortex, its entrainment – and observed frontal representation – may be modulated my Glu/ GABA interactions across distributed cortical networks.

The ASSR is generated by interacting GABAergic inhibition and rebound excitation in the auditory cortex, which propagates and entrains gamma oscillations observed in the frontal cortex. Additionally, the GABAergic system undergoes significant maturation during adolescence (Kilb, 2012; Caballero and Tseng, 2016; Silveri et al., 2013; Perica et al., 2022; Caballero et al., 2014b). Therefore, we hypothesize that the 40 Hz ASSR may provide insights into the underlying consequences of excitation/inhibition (E/I) balance across the cortex, indirectly reflecting systemic changes in GABAergic signaling that are relevant to frontal regions. Previous developmental studies have found increases in evoked power from 40 Hz auditory stimuli from ages 5–52 (Rojas et al., 2006) and ages 19–45 (Poulsen et al., 2009), revealing an inverted-U trajectory. This pattern is thought to reflect the interplay between opposing developmental effects: the increases in α1 GABA receptors promoting gamma activity, increasing the evoked activity, and the later synaptic pruning of pyramidal cell excitation (Cho et al., 2015a), consequently decreasing the evoked activity. Furthermore, previous studies have found resting state power, or spontaneous power, to decrease across all frequency bands from early to late childhood (Miskovic et al., 2015), supporting evoked activity, thus increasing cortical SNR, that may be reflecting circuitry plasticity (Larsen and Luna, 2018; Toyoizumi et al., 2013a; Fagiolini and Hensch, 2000). Throughout the manuscript we refer to the resulting cortical SNR in the PFC, driven by both auditory entrainment and attentional modulation, as 'PFC SNR'.

Given that inhibitory circuitry maturation regains E/I balance, and increases cortical SNR during animal model CPs (Hensch and Fagiolini, 2005), we hypothesized cortical SNR would increase with age, driven by increases in evoked power and decreases in spontaneous activity, as measured by the ASSR task. In this study, we collected a large, multimodal, longitudinal dataset with EEG and 7T Magnetic Resonance Spectroscopic Imaging (MRSI) of PFC, to investigate developmental changes in cortical SNR and its association with the E/I balance. We have previously showed neuroimaging evidence for increases in Glu/-GABA balance into adulthood in PFC (Perica et al., 2022; McKeon et al., 2024). Thus, we hypothesized that age related increases in E/I balance would be associated with increases in cortical SNR, derived from a 40 Hz stimuli auditory steady state task. In line with this hypothesis, we found developmental increases in PFC cortical SNR, driven by decreases in spontaneous activity, where SNR was found to be significantly associated with increases in PFC E/I balance. Finally, we show that increases in cortical SNR and decreases in spontaneous activity were associated with age related behavioral improvements in accuracy and latency variability in the memory guided saccade task. Taken together, this study provides *in vivo* evidence for CP plasticity mechanisms, i.e. increases in the E/I balance driving increases in cortical SNR, in the PFC through adolescence supporting stable and efficient circuitry and ultimately cognitive development.

2. Methods

2.1. Participants

Data was collected on 164 participants (87 assigned female at birth), between 10 and 32 years of age. Participants were recruited as part of an accelerated longitudinal cohort design with up to 3 visits at approximately 18mo intervals. Each time point consisted of three visits: a behavioral (in-lab) session, a 7T MRI scan, and an EEG session, typically occurring on different days within 1–2 weeks, for a total of 347 visits. Following data quality control and exclusion criteria, as described below, the final dataset included 283 sessions. Participants were recruited from the greater Pittsburgh area and were excluded if they had a history of loss of consciousness due to a head injury, non-correctable vision problems, learning disabilities, a history of substance abuse, or a history of major psychiatric or neurologic conditions in themselves or a first-degree relative. Patients were also excluded if any MRI contradictions were reported, including but not limited to, non-removable metal in their body. Participants or the parents of minors gave informed consent with those under 18 years of age providing assent. Participants received payment for their participation. All experimental procedures were approved by the University of Pittsburgh Institutional Review Board and complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964).

2.2. Data acquisition and preprocessing

2.2.1. Electrophysiological (EEG) data

Concurrent EOG (electrooculogram) and high-impedance EEG was recorded using a Biosemi ActiveTwo 64-channel EEG system located in the PWPIC Psychophysiology Laboratory and the University of Pittsburgh. EEG sessions were conducted in an electromagnetically shielded room while stimuli were presented by a computer approximately 80 cm away from participants. EEG data was collected during our auditory steady state task where participants are presented with a 20, 30, and 40 Hz click train. Initial auditory data was sampled at 1024 Hz and resampled at 512 Hz during preprocessing. Scalp electrodes were referenced to external electrodes corresponding to the mastoids due to its proximity to the scalp and low signal recording. An initial bandpass filter was set to 0.5 – 70 Hz. Data were preprocessed using a revised processing pipeline compatible with EEGLAB (Delorme and Makeig, 2004), which removed flatline channels (maximum tolerated flatline duration: 8 seconds), low-frequency drifts, noisy channels (defined as more than 5 standard deviations from the average channel signal), short spontaneous bursts, and incomplete segments of data. Deleted channels were replaced with interpolated data from surrounding electrodes. The resulting data was referenced to the average reference. As a final preprocessing step, independent component analysis (ICA) was performed to isolate and identify sources of artifacts within the EEG data, specifically focusing on those related to eye-blink activity. By identifying and removing these components, we minimized non-neural contributions, such as muscle movements and eye blinks, which can otherwise interfere with the clarity of neural signals. This step helped ensure that the resulting data more accurately reflected underlying neural activity, improving the precision of subsequent analyses.

2.2.2. Magnetic resonance spectroscopy

MRSI methods have been previously reported in Perica et al. (2022). Briefly, data were acquired at the University of Pittsburgh Medical Center Magnetic Resonance Research Center using a Siemens 7 T scanner. Structural images were acquired using an MP2RAGE sequence (1 mm isotropic resolution, TR/TE/flip angle 1/ flip angle 2: 6000 ms/2.47 ms/40/50). MRSI including GABA and glutamate were acquired using a J-refocused spectroscopic imaging sequence (TE/TR = 2 ×17/1500 ms) and water suppression was performed using a broad band semi-selective refocusing pulse and frequency selective inversion recovery (Pan et al., 2010). Radiofrequency (RF) based outer volume suppression was used to minimize interference in the signal from extracerebral tissue (Hetherington et al., 2010). An 8 × 2 1 H transceiver array using 8 independent RF channels was used to acquire data. High order shimming was used to optimize homogeneity of the B0 magnetic field. The 2D CSI oblique axial slice was acquired with conventional rectangular phase encoding of 24 × 24 over a FOV of 216 × 216 mm (10 mm thick, 0.9 ×0.9 ×1.0 cm nominal resolution), and was

positioned to include Brodmann Area 9 and pass through the thalamus. Methodological representation can be seen in Fig. 3A.

2.2.3. Auditory steady state task

Participants were presented with a blank screen and an auditory train of clicks in stereo via over-ear headphones. The stimulus was presented in blocks of 150 trials, each of which consisted of a 500 ms click train followed by 605 ms of silence. Blocks contained either ten 20 Hz clicks, fifteen 30 Hz clicks, or twenty 40 Hz clicks. Block order was randomly assigned (e.g., 30–40–20) for each participant at each session. The task was written in and executed by NBS Presentation software.

2.2.4. Memory guided saccade task

As reported in our previous studies (McKeon et al., 2023a), participants performed a memory guided saccade (MGS) task to assess working memory performance during the EEG session. Participants performed 3 runs of the MGS task, each containing 20 trials comprised of a visual guided saccade (VGS) to a peripheral cue, variable delay epoch (6–10 sec) where the participant must maintain the location of the peripheral target in working memory, followed by a memory guided saccade (MGS) to the remembered location. Task performance was assessed based on horizontal electrooculogram (hEOG) channels recorded from facial muscles (see acquisition details below). These were used to calculate VGS & MGS response latencies, as the time difference between the beginning of the recall epoch and the initiation of the VGS and MGS eye movements respectively, and saccadic accuracy, measured as the closest stable fixation point during the recall period to the fixated location during the initial visually guided fixation epoch. Visual representation of the task can be seen in Fig. 4A.

2.3. Data analysis

2.3.1. EEG analyses

2.3.1.1. Cortical signal-to-noise ratio (SNR). Cortical signal-to-noise ratio (SNR) was computed by calculating the evoked (stimulus-locked) and total power during the 20, 30, and 40 Hz click train frequency conditions. Prestimulus values (-200–0 ms) were extracted to provide a baseline reference. A task epoch was then defined over the first 800 ms following stimulus onset, and the auditory steady state response (ASSR) was computed for each electrode based on methods based on previous literature (Hirano et al., 2015; Tada et al., 2023; David et al., 2006; Hirano et al., 2020). Briefly, a Fast Fourier Transform (FFT) was applied to each single-trial epoch, resulting in per-trial power spectra. Power spectra were then averaged across trials to compute total power as a function of frequency. Evoked power was then derived by averaging the single trial time courses and calculating the resulting power spectra using FFT. By averaging across trials, only activity which was consistently timed relative to the stimulus onset remained, providing an estimate of the stimulus-evoked power. Spontaneous power was then derived by subtracting the evoked power from the total power. Finally, SNR was calculated as the ratio of evoked power to spontaneous power. A methodological representation of the method can be seen in Fig. 1.

2.3.1.2. Dimensionality reduction using PCA. Prior work has shown that ASSR is maximal at the frontal central electrodes Fz and FCz and then disperses amongst the frontal central electrodes surrounding it (Tada et al., 2016, 2023; Koshiyama et al., 2021a; Grent-'t-Jong et al., 2023; Spencer et al., 2009). To account for this spatial signal spread, we performed a principle component analysis (PCA) to reduce the dimensionality of the data for each of the total, evoked, and spontaneous power, as well as SNR. Due to both prior work and our hypotheses regard prefrontal cortex plasticity, the PCA was restricted to frontal electrodes, that is, F3, F5, F7, F1, F2, F4, F6, F8, AFz, AF1, AF2, Fp1, Fp2, Fz, AF5, AF6 (per the 10–20 international system naming convention). In each case, the first principal component (PC) captured the bulk for the signal variance and was used for subsequent analyses (Fig. 2A).

2.3.2. MRSI analyses

Analysis details have been previously reported in Perica et al. (2022). Briefly, a 2D CSI oblique axial slice was acquired (TR/TE/flip angle: 2180 ms, 23 ms, 7°, voxel size = 2.0 ×2.0 ×2.0 mm), as outlined in Perica et al. (2022), to ensure that the dorsolateral prefrontal cortex (DLPFC) was included and angled to pass through the thalamus. Regions of interest included right and left DLPFC due to its role in working memory. LCModel was used to obtain estimates of individual metabolites (Provencher, 2001), including creatine (Cre), γ-aminobutyric acid (GABA), glutamate (Glu), and Glu/GABA ratio, among others. To characterize the development of Glu-GABA interactions, we use two complementary measures based on prior approaches. Given greater variability in Glu and GABA levels in younger compared to adult ages that undermine the ability to see age related changes in Glu/GABA ratio (Perica et al., 2022), we computed, the correlation between the absolute

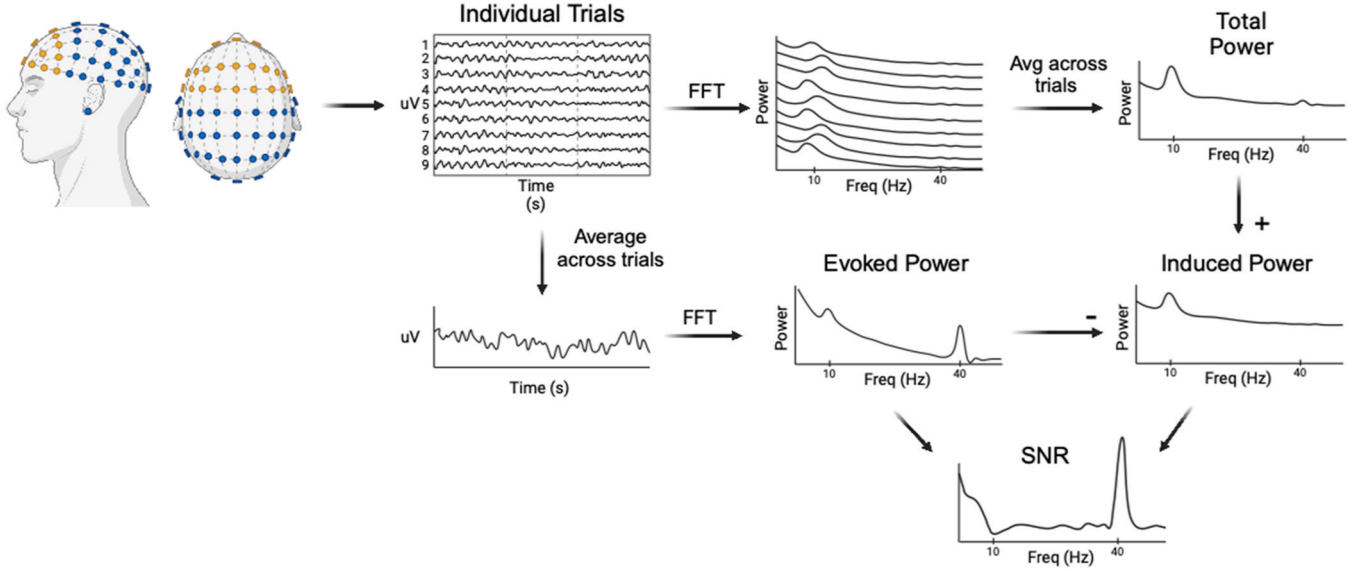

Fig. 1. Methodological representation for evoked power, spontaneous power, and cortical SNR.

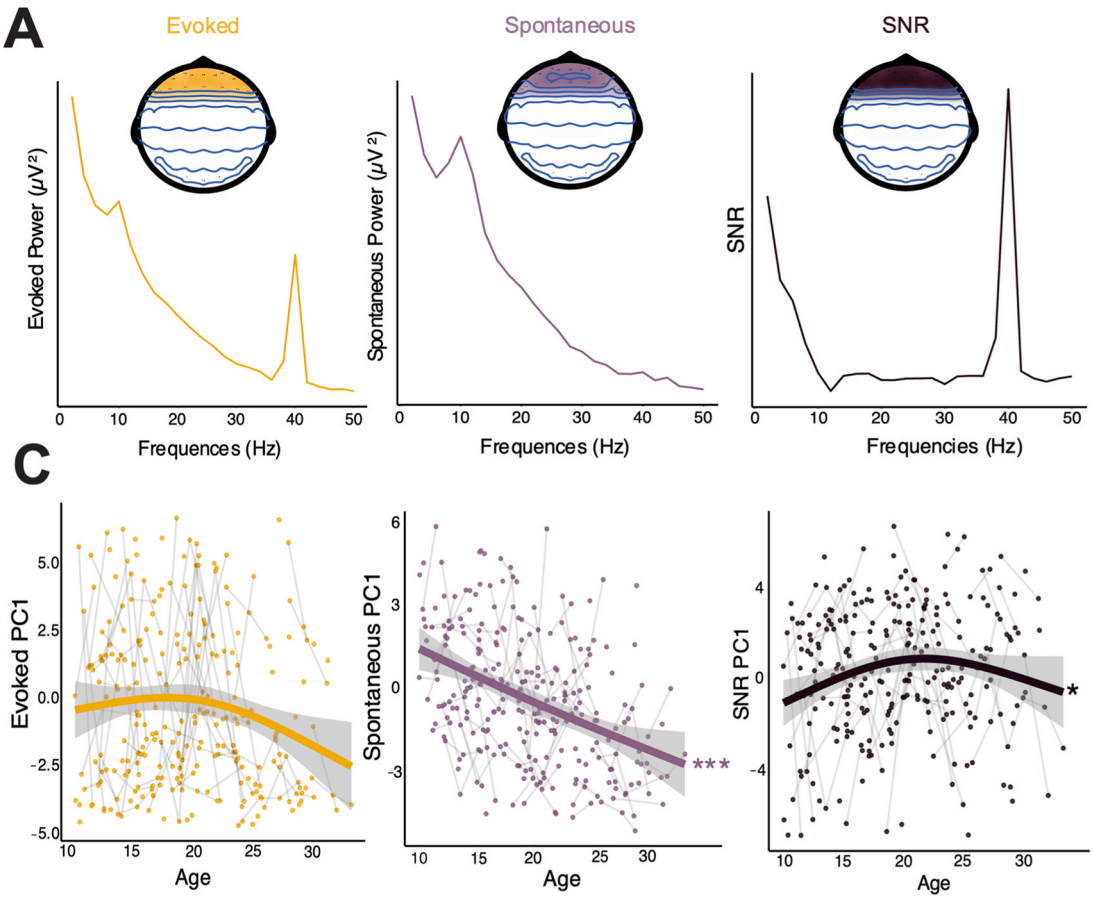

Fig. 2. A. Brain plots represent frontal ROI used for PCA. (Left) Evoked power by frequency. (Middle) Spontaneous power vs frequency. (Right) Cortical SNR vs frequency. **B.** (Left) Evoked activity PC1 values vs age (NS = p = 0.137). (Middle) Spontaneous activity PC1 values vs age. (Right) Cortical SNR PC1 values vs age. (* $p < 0.01$; ** $p < 0.001$; *** $p < 0.0001$).

value residual of the linear model of the association between Glu/Cr and GABA/Cr levels per-subject level. This measure captures the extent to which Glu and GABA levels align to population-level correlations between these metabolites (Steel et al., 2020; Rideaux, 2021), similar to how others have investigated Glu/GABA balance (Steel et al., 2020). Greater correlation between Glu and GABA levels thus, reflects greater symmetry/balance in contrast to asymmetry/imbalance when there are greater levels of one metabolite relative to another metabolite, (e.g., greater Glu in the presence of lower GABA). Based on a Kolmogorov-Smirnov test of normality, the Glu- GABA asymmetry was found to be non-normal (p = 4.39e-07). Thus, a square root correction was applied to improve normality (resulting p = 0.052).

2.3.3. Behavioral analyses

To characterize development of behavioral measures from the MGS task, including accuracy and response latency, we fit age-related performance effects using generalized additive mixed models (GAMMs) using the R package mgcv (Wood, 2017). Preliminary outlier detection was conducted on a trial level basis. Express saccades, in which eye movements were initiated within the first 100 ms after task onset were excluded, since these are believed to be primarily driven by subcortical systems without involving cortical processing of the visual cue (Luna et al., 2008). Position error measures greater than 23 degrees from the target were excluded as implausible since they exceeded the width of the screen. The remaining trials for each participant were combined, creating average performance measures and trial-by-trial variability measures for each participant. A separate model was performed for each of the behavioral measurements: MGS accuracy, MGS latency, as well as the trial-by-trial variability of each measure. Behavioral data from this task has been previously presented in McKeon et al. (2023b).

2.3.4. Statistical analyses

A threshold of 2 standard deviations from the mean was used to exclude statistical outliers for each electrode before the PCA. Due to missing data from outlier detection on each electrode, we imputed the missing data, using RStudio package mice (Buuren and Groothuis-Oudshoorn, 2011), for each subject so not to lose subjects who did not have complete data for all channels. Individual outliers were then detected using 2 standard deviations from the mean for each PC value for the evoked, spontaneous and SNR measures, as well as the MRSI derived measures, Glu, GABA, and Glu/GABA asymmetry.

To assess developmental trajectories of cortical SNR activity, we implemented GAMMs on the first principal component, PC1, of evoked power, spontaneous power, and SNR, including random intercepts estimated for each participant, while controlling for sex. We additionally tested for age-by-sex interactions while controlling for sex. Regression splines were implemented (3 degrees of freedom) to assess linear and non-linear effects (Wood, 2017, 2013). Auditory measures that were found to significantly change across adolescence were then used to test for associations with our MRSI measures, glutamate (Glu), GABA, and Glu GABA Asymmetry using linear mixed effect models (lmer function, lme4 package in Rstudio (Bates et al., 2015)). We first tested for significant main effects of the auditory measure on the MRSI parameter while controlling for age, hemisphere (left or right DLPFC), and sex. We additionally tested for auditory measure-by-age interactions while controlling for hemisphere. We then investigated whether our auditory measures had significant associations with our working memory measures (accuracy, accuracy trial variability, response latency, response

latency variability) using linear mixed effect models (lmer function, lme4 package in Rstudio (Bates et al., 2015)), while controlling for sex.

3. Results

3.1. Cortical SNR increases across adolescence

Auditory activity was first extracted to assess the validity of our task. Evoked activity (Fig. 2A Left) was found to peak at the frequencies corresponding to the auditory stimuli (i.e. 20, 30 and 40 Hz), and in the case of the 20 Hz condition, a peak was also seen in the harmonic 40 Hz band (first harmonic). Spontaneous activity (Fig. 2A Middle), derived from the difference between total and evoked activity, did not show these peaks at the corresponding frequencies, supporting the applied method for separating task-evoked from spontaneous activity. Cortical SNR, derived as the ratio of evoked activity/spontaneous activity, showed peaks at the corresponding frequencies to auditory stimuli and their related harmonic frequencies (Fig. 2A Right). To assess the developmental changes for each measure across adolescence, we tested for associations between age and each measure's first principal component. Evoked activity did not change with age ($F = 1.36$, $p = 0.151$; (Fig. 2B Left) or differ by sex ($\beta = 0.25$, $t = 0.88$, $p = 0.38$), and there was no age-by-sex interaction ($F = 0.019$, $p = 0.89$). In contrast, spontaneous activity showed significant decreases with age ($F = 37.4$, $p < 2e\text{-}16$; Fig. 2B Middle) and had no main effect of sex ($\beta = -0.04$, $t = -0.177$, $p = 0.85$). However, we did find a significant age-by-sex interaction on spontaneous activity ($F = 13.18$, $p = 0.00034$). Inspection of the sex-specific trajectories indicated similar age-related

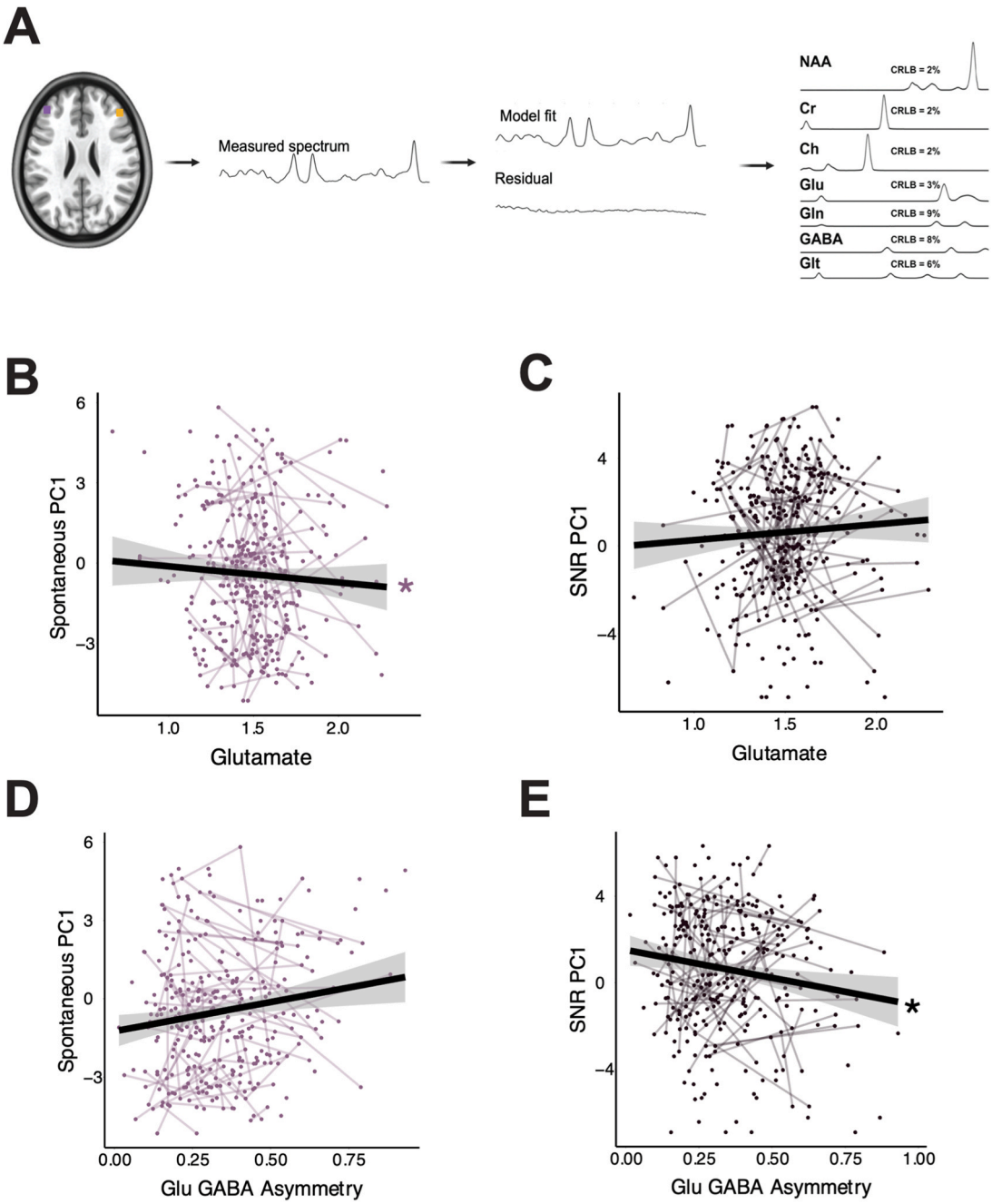

Fig. 3. A. Methodological representation of MRSI to measure glutamate and GABA. **B.** Spontaneous activity PC1 values vs glutamate. **C.** SNR activity PC1 values vs glutamate. **D.** Spontaneous activity PC1 values vs Glu GABA Asymmetry **E.** Cortical SNR PC1 values vs Glu GABA Asymmetry. (* $p < 0.01$).

decreases were present across sexes, with interactions driven by a difference in the timing and shape of developmental trajectories (see Supplemental Figure 1), where females stabilize earlier and males continue to show linear decreases in spontaneous activity across age. Reductions in spontaneous firing consequently led to increases in cortical SNR was found to increase through adolescence ($F = 4.55$, $p = 0.046$; Fig. 2B Right). No main effect of sex across age for cortical SNR was found ($\beta = 0.08$, $t = 0.28$, $p = 0.77$), nor a sex-by-age interaction ($F = 1.46$, $p = 0.227$).

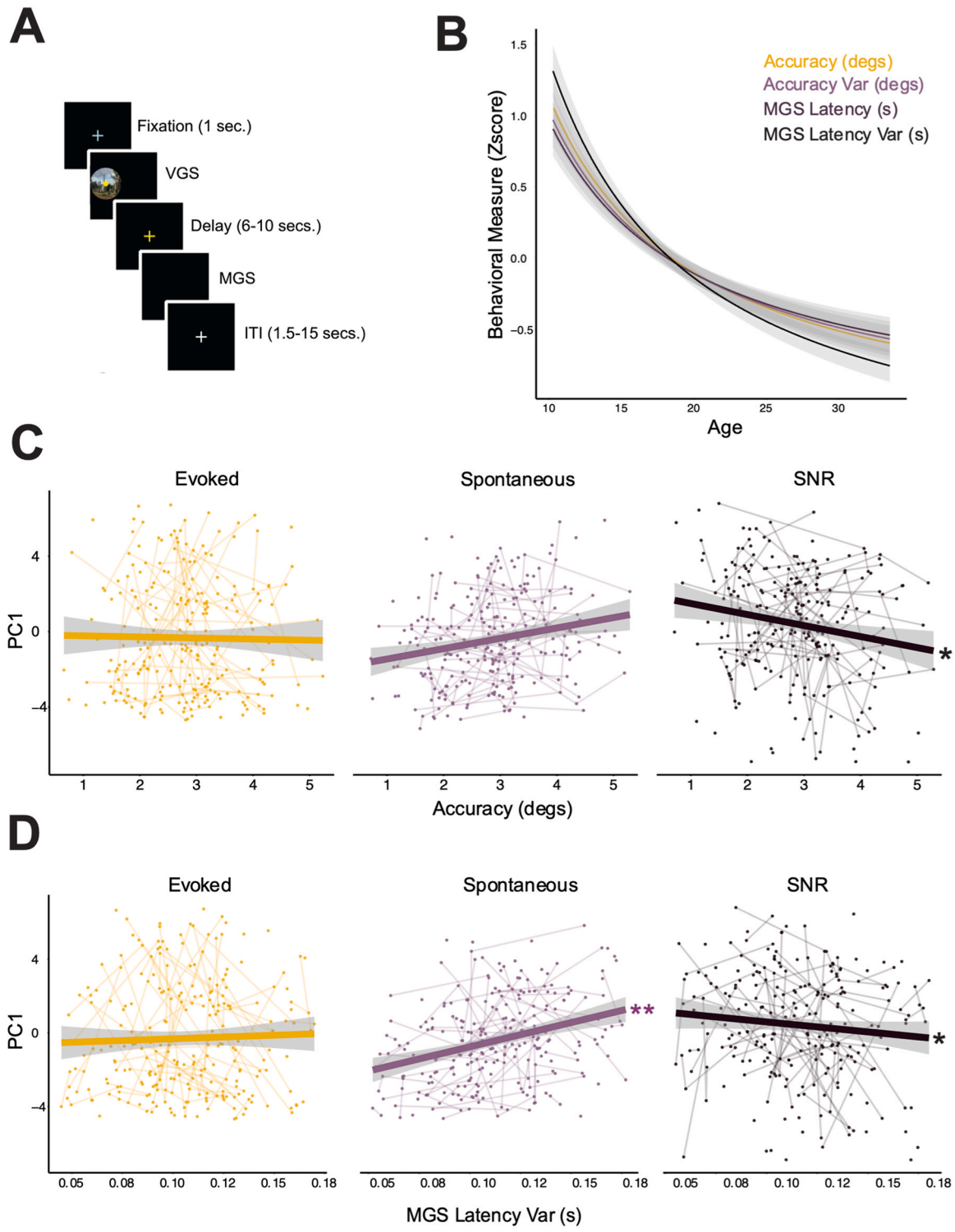

Fig. 4. A. Memory guided saccade task used to assess working memory. **B.** Working memory performance measures (accuracy, accuracy variability, response latency, and response latency variability) across age. Previously reported in McKeon, 2024 (McKeon et al., 2024). **C.** Auditory measures, evoked activity (left) (NS $p = 0.27$), spontaneous activity (middle) (NS $p = 0.16$), and cortical SNR (right) vs accuracy (measured as degrees away from intended target). **D.** Auditory measures, evoked activity (left), spontaneous activity (middle), and cortical SNR (right) vs trial-by-trial variable of response latency (measured as degrees away from intended target). (** $p < 0.001$; * $p < 0.01$).

3.2. Associations between cortical SNR and MRSI

To test if cortical SNR ratio is associated with MRSI-derived measures of E/I balance, we assessed relationships between EEG-derived ASSR task measures and Glu, GABA, and Glu-GABA asymmetry. All statistics were conducted controlling for age and hemisphere (left vs right DLPFC). Greater Glu was associated with less spontaneous activity ($\beta = -0.015$, t = -2.28, $p = 0.023$; Fig. 3B) while age-by-spontaneous activity interaction was not significant ($\beta = -0.001$, t = -1.41, $p = 0.16$). There was a significant main effect of hemisphere ($\beta = -0.08$, t = -3.78, $p = 0.002$) such that the LDLPFC has higher glutamate then the RDLPFC, but no main effect of sex ($\beta = -0.02$, t = -1.08, $p = 0.28$). Glutamate was not associated with cortical SNR ($\beta = 0.006$, t = 1.24, $p = 0.66$; Fig. 3C), nor a significant age-by-SNR interaction ($\beta = 2.206e-04$, t = 0.267, $p = 0.78$). Increases in Glu/GABA balance were associated with greater SNR in the PFC ($\beta = -0.007$, t = -2.38, $p = 0.017$; Fig. 3E) but did not have a significant age-by-SNR interaction ($\beta = 0.12$, t = 1.02, $p = 0.31$), nor a significant main effect of hemisphere ($\beta = -0.02$, t = -1.04, $p = 0.29$), nor sex ($\beta = 0.007$, t = 0.599, $p = 0.55$). Further analysis showed that Glu/GABA balance was not significantly associated with spontaneous activity ($\beta = 0.005$, t = 1.175, $p = 0.72$; Fig. 3D), nor was there a significant age-by-balance interaction ($\beta = -0.07$, t = -0.83, $p = 0.41$). As expected, due to age related changes in metabolite level variability, we did not find any associations ASSR measures and Glu/GABA ratio (See Supplement).

3.3. Associations between cortical SNR and working memory

An essential aspect of adolescent development involves the ongoing enhancement of executive functions, such as working memory, believed to rely on balance within excitatory/inhibitory (E/I) circuitry (Lim and Goldman, 2013) and signal-to-noise ratio (SNR) of cortical circuits (Toyoizumi et al., 2013b; Larsen et al., 2022). To assess whether SNR was related to improvements in executive function, we investigated the associations between cortical SNR and working memory, based on performance on the memory guided saccade (MGS) task. We found that greater PFC SNR was associated with better performance accuracy (measured as degrees away from the intended target) ($\beta = -0.48$, t = -2.36, $p = 0.019$; Fig. 4C Right). Neither evoked ($\beta = -0.24$, t = -1.06, $p = 0.28$) or spontaneous ($\beta = 0.18$, t = 1.26, $p = 0.21$) activity was significantly associated with performance accuracy. Meanwhile, we found the trial-by-trial response latency variability increased with spontaneous activity ($\beta = 14.7$, t = 2.85, $p = 0.005$; Fig. 4D Middle) and with decreases in PFC SNR ($\beta = -16.34$, t = -2.23, $p = 0.03$; Fig. 4D Right). Spontaneous activity did not have a significant age-by-latency variability interaction ($\beta = 0.93$, t = 1.07, $p = 0.28$) nor did PFC SNR ($\beta = -0.47$, t = -0.38, $p = 0.68$). (Additional behavioral measures, accuracy trial variability and MGS response latency can be found in Supplement Fig. 3. Additional statistics can be found in Supplement Table 1).

4. Discussion

This study aimed to investigate auditory driven SNR in the PFC using EEG and its associations with the E/I balance via MRSI measures of GABA and Glu, as a mechanism of CP plasticity during adolescence. Previous animal studies investigating sensory cortex CPs has shown that maturation of the GABAergic inhibitory system supports the suppression of spontaneous, asynchronous activity, in favor of evoked, synchronous activity, increasing the cortical SNR (Hensch, 2005; Toyoizumi et al., 2013a; Hensch and Fagiolini, 2005). Consistent with these CP mechanisms, we found that PFC cortical SNR, during a 40 Hz auditory steady state task, increases across adolescence, driven by significant decreases in spontaneous activity. Furthermore, we found increases in PFC SNR to be associated with increases in the DLPFC Glu/GABA balance. Post-hoc analyses suggested this association is driven by the significant relationship between increases in spontaneous activity and decreases in glutamate. To interrogate the developmental effects of PFC SNR on behavior, we assessed working memory via a memory guided saccade (MGS) task, results of which have previously been reported (McKeon et al., 2023a, 2024). Here, we found increases in cortical SNR to be correlated with increases in performance accuracy suggesting that fidelity of the mnemonic information is supported by optimal SNR. While decreases in spontaneous activity and increases in cortical SNR were found to be associated with decreases in performance latency variability, suggesting that performance stability is supported by both high SNR and associated decreases in spontaneous neural function. Taken together, these results suggest developmental increases in PFC SNR, driven by decreases in spontaneous activity, may be due to developmental increases in Glu/GABA balance, and support the development of higher order cognitive functions through adolescence into adulthood.

Previous work has shown that the auditory steady state task elicits robust gamma oscillations driven by 40 Hz stimulus clicks, thought to be driven by GABAA receptors (Lewis et al., 2005) via cycling through inhibition and rebound excitation (Vohs et al., 2010; Gonzalez-Burgos and Lewis, 2008). Furthermore, the ASSR is strongest at central electrodes Fz and FCz, with activity dispersing throughout the frontal electrodes (Tada et al., 2016, 2023; Koshiyama et al., 2021a; Grent-'t-Jong et al., 2023; Spencer et al., 2009). Given that the GABAergic system undergoes significant maturation through adolescence in the PFC (Caballero et al., 2014a; Hoftman et al., 2015; Fung et al., 2010; Lewis et al., 2005; Erickson and Lewis, 2002; Hoftman and Lewis, 2011), we hypothesized that the frontal ASSR should change developmentally. Consistent with this hypothesis, previous developmental studies have found increases in evoked power from 40 Hz auditory stimuli from ages 5–52yo (Rojas et al., 2006) and 19–45yo (Poulsen et al., 2009), with a study spanning ages 8–22 identifying an inverted-U trajectory (Cho et al., 2015b). These studies however found the most significant changes in young childhood, roughly ages 5–10 years old, in contrast to our older cohort of 10–32 years of age, suggesting that evoked activity may mature in childhood. These patterns of evoked power across development are thought to reflect the interplay between opposing developmental effects: the increases in α1 GABA receptors promoting gamma activity, thus increasing evoked activity, and the later synaptic pruning of pyramidal cell excitation (Cho et al., 2015a), which in PFC, begins in childhood continuing through adolescence (Huttenlocher and Dabholkar, 1997), thus decreasing the evoked activity.

Spontaneous activity is conceptually similar to brain activity during resting state, that is, activity that is not locked to any task stimuli. Trial-by-trial power variations during tasks (Wainio-Theberge et al., 2021; Myers et al., 2014), and non-stimulus-locked activation during auditory steady state (Tada et al., 2023) decrease across adolescence in all frequency bands (McKeon et al., 2023a, 2024; Whitford et al., 2007; Tierney et al., 2013; Anderson and Perone, 2018; Matousek and Petersén, 1973). Here, we sought to assess spontaneous activity, sometimes referred to as induced activity, that is non-stimulus-locked, across adolescence, during a 40 Hz auditory steady state task. Excitatory activity is thought to be driven by NMDA- mediated activation on PV positive interneurons, triggering postsynaptic potentials, and generating gamma oscillations (Sohal et al., 2009; Carlén et al., 2012; Buzsáki et al., 2012). Here, we found highly significant decreases in spontaneous activity across age, which may be indicative of PV+ interneuron maturation that has been found to suppress spontaneous firing (Hensch, 2005; Toyoizumi et al., 2013a; Hensch and Fagiolini, 2005). Furthermore, NMDA subunit NR2B density, which increases in transmodal cortices (Burt et al., 2018; Wang et al., 2008) at the beginning of a critical period, begins to decrease as the critical period closes (Erisir and Harris, 2003), which may further explain the decrease in spontaneous firing, constrained by the shortening of the time course of excitatory synapses. This switch from spontaneous to evoked power has been suggested to increase cortical SNR across adolescence, due to PFC PV positive basket cells ability to innervate pyramidal neurons on their soma allow them to

synchronize activity between cortical networks (Katz and Shatz, 1996; Toyoizumi et al., 2013b). We then calculated cortical SNR as the ratio between evoked activity and spontaneous activity and found significant increases across adolescence. These results suggest PFC is undergoing similar mechanisms as sensory system CPs, but in adolescence such as the maturation of PV+ interneuron circuitry maturation (Katz and Shatz, 1996; Toyoizumi et al., 2013b), and excitatory circuitry maturation, promoting CP plasticity (Katagiri et al., 2007; Fagiolini et al., 2004).

In our previous work we have shown developmental decreases in MRSI derived levels of glutamate and increases in the Glu/GABA balance (McKeon et al., 2024) throughout adolescence into adulthood. Here, we sought to investigate whether these measures of the E/I balance would be associated with our EEG derived measures of cortical SNR. Indeed, we find increases in Glu/GABA balance, measured as a decrease in the Glu/GABA asymmetry, to be significantly associated with increases in cortical SNR. Post-hoc analyses showed that this relationship may be underlined by the significant association, when controlling for age, where ultimately decreases in spontaneous activity in PFC are associated with increases in glutamate. While this result may seem counterintuitive, it may be representing the contrasting developmental mechanisms of strengthening synaptic connections, network integration, and sustained excitatory activity (Wang et al., 2020; Sydnor et al., 2021; Hilgetag et al., 2019), all while the cortex undergoes significant synaptic pruning (Huttenlocher and Dabholkar, 1997; Simmonds et al., 2014). Furthermore, the NMDA subunit change during adolescence (Burt et al., 2018; Wang et al., 2008) first supports excitatory activity (Wang et al., 2020; Sydnor et al., 2021; Hilgetag et al., 2019) via glutamate, but as the CP begins to close, the subunit density decreases and maintains a low level in adulthood, thus contributing to decreases in excitation (Erisir and Harris, 2003). These complex and contrasting developmental mechanisms need to be further investigated.

A key part of adolescent development is the continued refinement of executive functions (Tervo-Clemmens et al., 2023), including working memory, thought to be supported by increasing E/I balance (Lim and Goldman, 2013), which in turn supports a high cortical SNR (Toyoizumi et al., 2013b; Larsen et al., 2022). Accuracy and latency in working memory are unique components underlying executive function, where accuracy reflects the fidelity of the mnemonic information being kept in working memory, while latency reflects the speed of cognitive information processing (Tervo-Clemmens et al., 2022; Ravindranath et al., 2022). Further, the DLPFC, the region of interest used in our MRSI data, is a region known to be involved in visual spatial memory (Goldman-Rakic, 1995). As we previously reported (McKeon et al., 2024), working memory accuracy, trial-by-trial accuracy variability, response latency, and trial-by-trial response latency show improvements into adulthood. Here, we compared these behavioral results to our measures of evoked, spontaneous activity, and entrained cortical SNR. We found performance accuracy improved with increasing cortical SNR. We also found decreases in trial-by-trial response latency variability to be associated with decreases in spontaneous activity and increases in cortical SNR. These results suggest that age-related improvement in accuracy may be due to the E/I balance maximizing signal efficiency of neural responses via local gain control on excitatory circuitry (Ferguson and Gao, 2018; Buschman, 2021) while increases in the speed of generating a response may reflect stabilization of optimal processing.

CP mechanisms result in neural circuitry that has high SNR to a given input and responds with a synchronous, consistent output sending activity with high SNR to downstream circuits (Larsen and Luna, 2018). To perform higher order cognitive functions, such as in working memory, areas that integrate sensory information, such as the PFC, require stable inputs. During adolescence, sensory systems are providing high SNR output to downstream circuits that support task performance, like the PFC. Thus, our results suggest that with maturation the PFC integrates multisensory input into stable and consistent activity, reflected in increasing cortical SNR and greater E/I balance, resulting in enhanced ability to maintain accurate information online. This may be achieved through maximizing signal efficiency of neural responses via local gain control on excitatory circuitry (Ferguson and Gao, 2018; Buschman, 2021). Furthermore, high SNR drives consistent stimulus- evoked activity and suppresses spontaneous activity. Thus, response latency variability improvements being associated with reductions in spontaneous activity may suggest that activity stabilizes and becomes more reliable as synaptic pruning establishes optimal circuitry.

While our study provides valuable insights into the relationship between PFC SNR in the PFC and our MRSI-derived measures of E/I balance, several limitations must be acknowledged. First, our measure of cortical SNR in the PFC is derived from activity in the auditory cortex that propagates through volume condition to measurable activity in the frontal cortex. Additionally, while we propose that the observed changes in SNR are linked to increases in Glu/GABA balance, via our measure of Glu/GABA asymmetry, the complex mechanisms underlying cortical plasticity during adolescence still need to be fully understood. Furthermore, it is worth noting that while our cortical SNR measure is primarily driven by the auditory cortex, our spectroscopy is directly measured from the DLPFC. However, the interplay between GABAergic interneurons and excitatory pyramidal neurons in necessary for the gamma entrainment observed in the PFC (Ferguson and Gao, 2018; Cho et al., 2015a; Buzsáki and Wang, 2012; Lally et al., 2014). Therefore, despite the indirect relationship between the auditory-driven SNR and the neurochemical measures from the DLPFC, understanding this interplay enhances our interpretation of how E/I balance may influence cognitive processes during adolescence. Future research would benefit from incorporating more direct measures of cortical SNR in the PFC, utilizing techniques such as transcranial magnetic stimulation (TMS) to elicit evoked and spontaneous power and ultimately cortical SNR. Furthermore, it is worth noting using cortical SNR in the PFC via entrainment from the auditory cortex has limitations regarding its use as a proxy for PFC function and its associations with cognitive function, given that it is an indirect measure. However, the entrainment of gamma oscillations in the PFC via auditory stimuli is still dependent on the oscillatory activity between GABAergic interneurons and excitatory pyramidal neurons (Ferguson and Gao, 2018; Cho et al., 2015a; Buzsáki and Wang, 2012; Lally et al., 2014), and have been shown to be involved in higher order cognitive functions, such as working memory (Lim and Goldman, 2013). Furthermore, increases in cortical SNR facilitates neural population synchronization (Hensch, 2005; Toyoizumi et al., 2013a; Hensch and Fagiolini, 2005) which supports executive function by stabilizing task-evoked activity (Tervo-Clemmens et al., 2023; Montez et al., 2017; Simmonds et al., 2017; Alloway et al., 2006; Luna et al., 2004; Geier et al., 2009; McKeon et al., 2023a). Therefore, the entrainment observed in the PFC should reflect the general strength of gamma oscillations and increases in cortical SNR driven by the auditory cortex, which can contribute to enhanced executive functioning. Together, these results provide *in vivo* evidence that PFC SNR increases as the E/I circuitry becomes balanced, supporting the refinement and integration of multipart sensory input into a stable and reliable circuitry that can perform complex executive functioning. Importantly, CP mechanisms can inform the basis of refinements in higher-order cognition and provide context for structural and functional maturation during adolescence (Larsen and Luna, 2018). Furthermore, these results are in line with a model of adolescent PFC CP plasticity (Luna et al., 2015), as well as, build off our previous work on the aperiodic component as a measure of E/I balance and CP plasticity during adolescence (McKeon et al., 2024). Importantly, these results provide possible mechanisms for plasticity in normative development but also in impaired development, such as in psychopathology, which predominantly emerges in adolescence (e.g., psychosis, mood disorders, addiction) (Blakemore and Mills, 2014; Steinberg, 2008), is associated with limitations in cognition (O'Donnell et al., 2013; Poulsen et al., 2009; Chavez-Baldini et al.), and with impairments in excitatory and inhibitory processes (O'Donnell et al., 2013; Lewis et al., 2005; van Bueren et al., 2023; Selten et al.,

2018; Gonzalez-Burgos et al., 2010).

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CRediT authorship contribution statement

Beatriz Luna: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Chan-Hong Moon:** Software, Resources, Methodology, Data curation. **Hoby Hetherington:** Software, Resources, Methodology, Data curation. **Will Foran:** Software, Resources, Project administration, Data curation. **Finnegan J. Calabro:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Maria I. Perica:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shane McKeon:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2024.102695.

Data availability

Data will be made available on request.

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