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Title: Changes in gamma bursts supporting working memory development through adolescence derived from EEG spectral processing

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ABSTRACT

Adolescence is a stage of development characterized by neurodevelopmental specialization of cognitive processes. In particular, working memory continues to improve through adolescence, with increases in response accuracy and decreases in response latency continuing well into the twenties. Human electroencephalogram (EEG) studies indicate that gamma oscillations (30-75 Hz) during the working memory delay period support the maintenance of mnemonic information guiding subsequent goal driven behavior, which decreases in power with development. Importantly, recent electrophysiological studies have shown that gamma bursts, and not sustained activity, reinstate working memory during the delay period. Developmental changes in gamma bursts during working memory, have not been studied. Thus, we used EEG in conjunction with a novel spectral event processing approach to investigate age-related changes in transient gamma band activity during a memory guided saccade (MGS) task in 164 10- to 30-year-olds. As expected, accuracy improved, and latency decreased with age. EEG results indicated robust age-related decreases in mean gamma power and the number of gamma band events during both the working memory delay epoch but also the fixation epoch before working memory encoding, suggesting age-related change in core aspects of information processing. Relationships between gamma events and behavior however were only evident during the working memory delay period and only during adolescence where more gamma events were associated with faster latency and trial level event variability was associated with latency variability. These results suggest a process of specialization where developmental decreases in gamma events into adulthood support working memory responses reflecting optimization of executive function.

1. INTRODUCTION

Working memory continues to improve through adolescence into adulthood[1,2] in parallel with brain structural maturation[2–4] and optimization of brain function[5,6]. Behavioral studies using verbal and visuospatial tasks have consistently shown that working memory accuracy and latency continue to improve well into the twenties[5,7]. Supporting this cognitive maturation, fMRI studies have found that while brain regions involved in working memory are online by childhood, there is a continued refinement and integration of specialized regions that lead to stabilized neural activity and an improvement in behavioral performance, such as latency and accuracy[5,6]. In particular, there is substantial evidence that in addition to overall improvements in working memory performance through adolescence, there are significant increases in the reliability with which individuals performed these functions. This has been seen as a reduction in the variability of trial-to-trial accuracy[5,6] and latency[5,6]. Based on this, it has been shown that while the whole brain patterns of activity associated with performance of a memory guided saccade (MGS) task do not change with age, the variability of the expression of whole brain patterns of activity decreases with age and is associated with behavioral performance stabilization[5], suggesting that stability of whole brain dynamics may be critical for understanding the maturation of working memory though adolescence.

Human electroencephalogram (EEG) and animal electrophysiological data have identified specific aspects of neural signal processing supporting working memory processes, including gamma oscillations in the dorsolateral prefrontal cortex (DLPFC)[6,8]. Historically, these gamma oscillations have been characterized as showing sustained activity throughout the delay period of working memory tasks in non-human primate and human studies[9–13]. However, recent human and non-human primate studies have shown that at the trial level, neural activity occurs in burst-like events, defined as transient bursts of neural activity where not only are the amplitude and frequency important, but the timing, duration, and rate of the bursts may play a key role in supporting higher order cognitive functions[9,14–18]. Working memory delay activity has since been shown to be non-stationary, with spiking occurring sporadically. Between these active states, working memories may be stored as temporary changes in synaptic weights through gamma band associated spiking[11,16,18,19].

EEG provides a non-invasive measure of electrical neural activity capable of characterizing different properties of neural signal processing, including gamma band oscillatory power and bursting activity, that can inform neural mechanisms underlying the improvement of working memory in adolescent populations. Developmental EEG studies have found that absolute EEG power decreases in most frequency bands from 10 to 20 years of age[20,21] and have been associated with decreases in gray matter volume across adolescence[21]. In particular, animal and human models show decreases in gamma band (30-75 Hz) power, which is associated with working memory[22], across adolescence[22,23]. However, to date no studies to our knowledge have leveraged EEG in developmental

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populations to characterize the trial-level spectral bursting activity associated with the maturation of working memory. Here, we use a novel EEG analysis pipeline[24] to define the developmental trajectory of gamma band bursts at the trial level and their association with working memory through adolescence.

2. METHODS

2.1 Participants

One hundred and sixty-four participants (87 assigned female at birth), between 10 and 32 years of age participated in this study (84 between 10-18, and 80 between 18-30). Participants were excluded if they had a history of head injury with loss of consciousness, a non-correctable vision problem, a history of substance abuse, a learning disability, or a history of major psychiatric or neurologic conditions in themselves or a first-degree relative. Participants were also excluded if they reported any MRI contraindications, such as non-removable metal in their body given other neuroimaging aspects of the broader project. Signed informed consent was obtained after discussing the study with the subject and/or their guardians. Parental/guardian consent was obtained for all subjects under the age of 18, as well as the subject's own consent regardless of age. For participants over the age of 18, participant consent was obtained. 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 Memory Guided Saccade Task

Participants performed a memory guided saccade (MGS) task to assess working memory (see Figure 1). The trial began with fixation to a blue cross for 1 sec. The participant was then presented with a peripheral cue in an unknown location along the horizontal midline (12.5 or 22.2 degrees from central fixation to left or right of center), where they performed a visually guided saccade (VGS) to the target and maintained fixation. Once the cue disappeared, the participant returned their gaze to the central fixation point and fixated for a variable delay epoch (6-10 sec) during which they were to maintain the location of the peripheral target. Once the central fixation disappeared the participant performed a memory guided saccade to the recalled location of the previous target. The trial ended when participants were presented with a white fixation cross that served as the ITI (1.5-15sec). Participants performed 3 runs of the MGS task, each containing 20 trials.

Task performance was assessed based on horizontal electrooculogram (hEOG) channels recorded from facial muscles (see acquisition details below). At the start of the session, participants performed a calibration procedure in which they fixated a series of 20 dots sequentially, positioned along the horizontal midline and spanning the width of the screen. These were used to generate a calibration curve relating hEOG voltage to horizontal screen position. Eye position during the MGS task was used to derive output measures using this calibration data by aligning hEOG signals to different task triggers. 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 fixation point during the recall period to the fixated location during the initial visually guided fixation epoch.

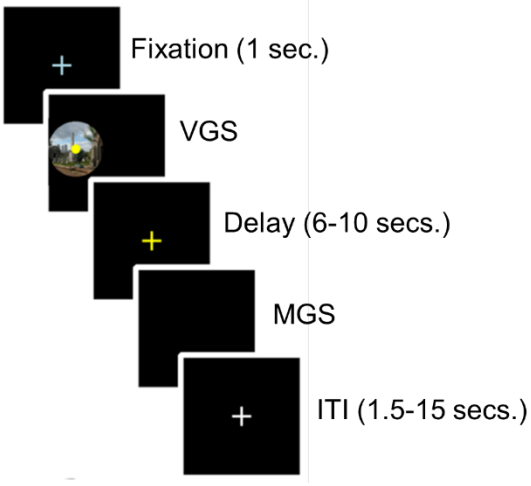

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Figure 1. Memory Guided Saccade Task. Epochs from top to bottom: Participants attend to a fixation cross. Once fixation is extinguished participants saccade to a peripheral dot stimulus on top of a scene (the scene is intended for a memory task of another aim of this project). After peripheral target is extinguished, participants attend to a yellow fixation cross while remembering the location of the previous target. When the fixation is extinguished, participants saccade to the location they remembered the target had been. An ITI with a fixation white cross occurs between trials.

2.3 Electrophysiological Data Acquisition and Preprocessing

Concurrent EOG and high-impedance EEG was recorded with a Biosemi ActiveTwo 64-channel EEG system located in an electromagnetically shielded room during the MGS task (described above). The task stimuli were presented by a computer 80 cm from the subject, and head position was maintained using a chin rest. Initial data was sampled at 512 Hz and down sampled to 150 Hz during preprocessing. Data was referenced to external electrodes corresponding to the mastoids due to their proximity to the scalp and low signal recording. An initial bandpass filter was set to 0.5-75 Hz. We used a revised version of an established protocol (https://sccn.ucsd.edu/wiki/Makoto's_preprocessing_pipeline, retrieved April 23, 2020) for preprocessing compatible with EEGLAB[25]. This protocol removes 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), large amplitude artifacts, and incomplete segments of data. Deleted channels were replaced with interpolated data from surrounding electrodes. Continuous signals were divided into epochs, time-locked to stimulus onset (~1-3s). Data epochs were cleaned with an amplitude threshold of -500 to 500μV to exclude eye blinks. The resulting data was baselined relative to the average reference. As a final preprocessing step, independent component analysis (ICA) was performed to identify eye-blink artifacts and remove their contribution to the data.

2.4 Spectral Analysis

A spectral events pipeline (https://github.com/jonescompneurolab/SpectralEvents) was applied to the preprocessed channel time courses to interrogate band-specific bursting activity. Spectra data was computed from 1 second data windows from the delay epoch of the task, comprised of seconds 3-4 to avoid artifact from preceding eye movements and preparation from an imminent response, and 1 second from the inter-trial fixation epoch. Time-frequency representations (TFRs) of the data were calculated from 1 to 75 Hz by convolving the signals with a complex Morlet wavelet of the form $\omega(t, f_0) = Aexp((-t\text{^}2/(2\sigma_t\text{^}2))) exp(2i\pi f_0 t)$, 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[15]. The TFR was normalized to the median power value for each frequency band, derived from all the power values within a specified stimulus window. Transient frequency events were found by retrieving local maxima in the un-normalized TFR and selecting suprathreshold peaks within the frequency band of interest and are reported as event number. Power of an event was derived from the normalized TFR value at each local maxima, defining a burst of activity, and calculated as factors of median (FOM). Event duration and frequency span are calculated as full- width- half- maximum from the burst maxima in the time and frequency domain, respectively. Trial average and trial-by-trial variability 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, respectfully.

2.5 Statistical Analysis

To examine age-related changes in behavioral measures, including accuracy and response latency, generalized additive models (GAMMs) were implemented using the R package mgcv[26]. Preliminary outlier detection was conducted on a trial level basis. Express saccades of less than 100ms, believed to be primarily driven by subcortical systems[27], were excluded. 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 subject. Finally, for group level analyses, outlier detection was performed, excluding subjects more than 2 SDs away from the mean. A separate model was performed for each of the behavioral measurements: MGS accuracy, MGS latency, and VGS latency, as well as the trial-by-trial variability of each measure. To correct for multiple comparisons between the six behavioral measures, Bonferroni correction was employed.

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To examine age-related trends in the gamma (30-75 Hz) frequency band during the delay and fixation epochs of the MGS task, GAMMs were implemented using the R package mgcv[26]. A separate model was performed for each of the spectral event measurements: power, duration, number of events per trial, as well as the trial-by-trial variability of each measure. Subjects' power was logarithmically transformed before being entered into the model. Trials greater than 2 SDs away from the variable mean were excluded. To correct for the six delay measures and the six fixation measures, Bonferroni correction was applied.

For all behavioral and spectral event measures showing significant age-related changes, we performed analyses to identify specific periods of significant age-related change. To do so, a posterior simulation was performed on the first derivative of the GAMM model fits. Consistent with previous work[26,28,29], 10000 simulated GAM fits and their derivatives (generated at age intervals of 0.1 years) were computed from a multivariate normal distribution; vector means and covariance of which corresponded to the fitted GAM parameters. Confidence intervals (95%) were generated from the resulting derivatives. The periods of age-related growth were derived from the ages corresponding to when the confidence interval did not include zero ($p < 0.05$).

To assess relationships between the significant age-related EEG activity and behavioral changes, GAMMs were implemented using the R package mgcv[26]. To determine if EEG-working memory responses occurred in an age-specific manner, we split our sample into under- and over-18yo groups to test for adolescent vs young adult effects separately. Each significant delay epoch spectral measure was tested against the memory guided saccade behavioral measures (accuracy, measured in degrees from the correct target location, and response latency), while each significant fixation epoch spectral measure was tested against and the visual guided saccade behavioral measures (response latency). To correct for the resulting six comparisons, Bonferroni correction was applied.

3. RESULTS

3.1 Behavioral Performance

As expected, behavioral performance improved with age for all MGS metrics including increased accuracy (p = 1.2e-15; Figure 2A), decreased response latency (p = 0.01; Figure 2B), and decreased trial-to-trial variability in both accuracy (p = 8.82e-07; Figure 2C) and response latency (p = 1.2e-15; Figure 2D). Significant developmental change was found to occur throughout adolescence (11-22 years of age) for MGS accuracy and 11-21 years of age for trial-by-trial variability for MGS accuracy (Figure 2A and 2C). MGS latency was found to have significant growth rates only in early adolescence (11-13 years of age), while decreases in MGS variability in latency continued into the twenties (Figure 2B and 2D). Visually guided saccade (VGS) response latency was found to trend downward with age ($p = 0.1$; Figure 3A) while trial-by-trial variability response latency ($p = 0.0014$; Figure 3A) was found to significantly decrease with age. Growth rates for VGS measures were found to occur from 13-17 for response latency and 11-18 for trial-by-trial variability of response latency (Figure 3).

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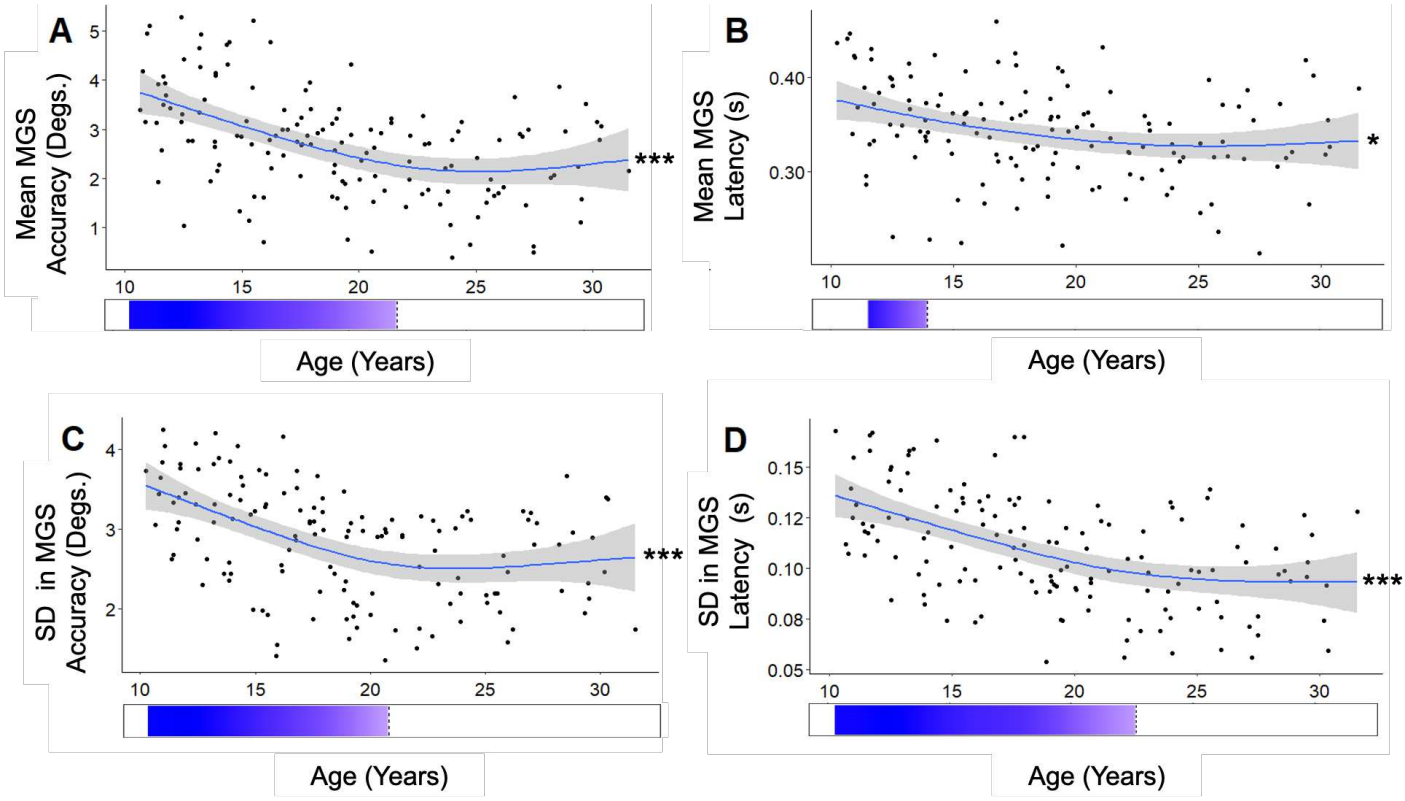

Figure 2. **A**. Mean MGS accuracy (degs.). Growth rates show significant rates of change between 11-22 years of age **B**. Mean MGS response latency (s). Growth rates show significant rates of change between 11-13 years of age **C**. Trial-by-trial variability in MGS accuracy (degs.). Growth rates show significant rates of change between 11-21 years of age **D**. Trial-by-trial variability of MGS response latency. Growth rates for show significant rates of change between 11-23 years of age. All by age in years. Purple bars indicate regions of significant age-related change in MGS performance based on the derivative of the GAM model fit. (* $p < 0.01$; ** $p < 0.001$; *** $p < 0.0001$)

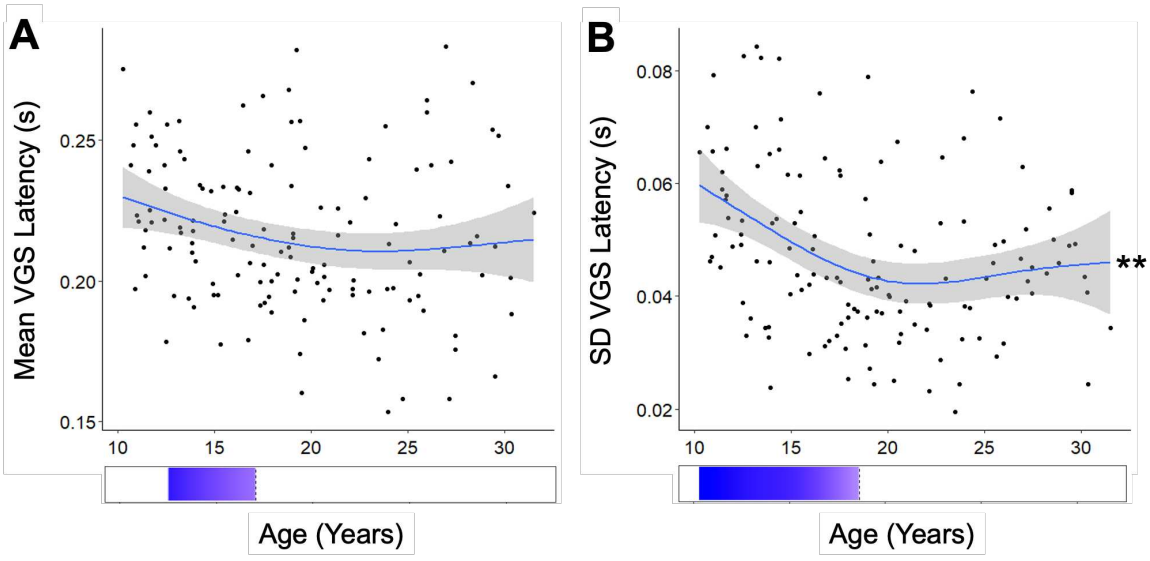

Figure 3. **A**. Mean VGS Response latency (s). Growth rates show significant rates of change between 13-17 years of age **B.** Trial-by-trial variability of VGS response latency. Growth rates show significant rates of change between 11-18 years of age. All by age in years. Purple bars indicate regions of significant age-related change in VGS performance based on the derivative of the GAM model fit. (** $p < 0.001$)

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3.2 Developmental Changes in EEG Spectral Event Measures

During the delay period of working memory task, trial power (p = 3.702e-06; Figure 5A), trial-by-trial trial power variability (p = 0.00065; Figure 5C), and the number of spectral events (p = 0.02; Figure 5B), all decreased across adolescence. No significant age-related change was identified for the trial-to-trial variability in the number of events, the duration of events, nor the trial-by-trial variability in the event duration (p > 0.05). Growth rates showed significant decreases from 10-21 years old for trial power (Figure 5A; red bar), 10-24 years old for trial power variability (Figure 5C; red bar), and 13-19 years old for the number of spectral events (Figure 5B; red bar)

Similarly, during the fixation epoch prior to trial onset, trial power (p = 1.2e-15; Figure 5A), trial-by-trial variability (p = 2.86e-05; Figure 5C), and event number (p = 0.005; Figure 5B) all decreased across age. Growth rates showed significant decreases from 11-24 years old for trial power (Figure 5A; purple bar), 10-24 years old for event number (Figure 5B; purple bar) and decreases for trial power variability continued through the twenties (Figure 5C; purple bar).

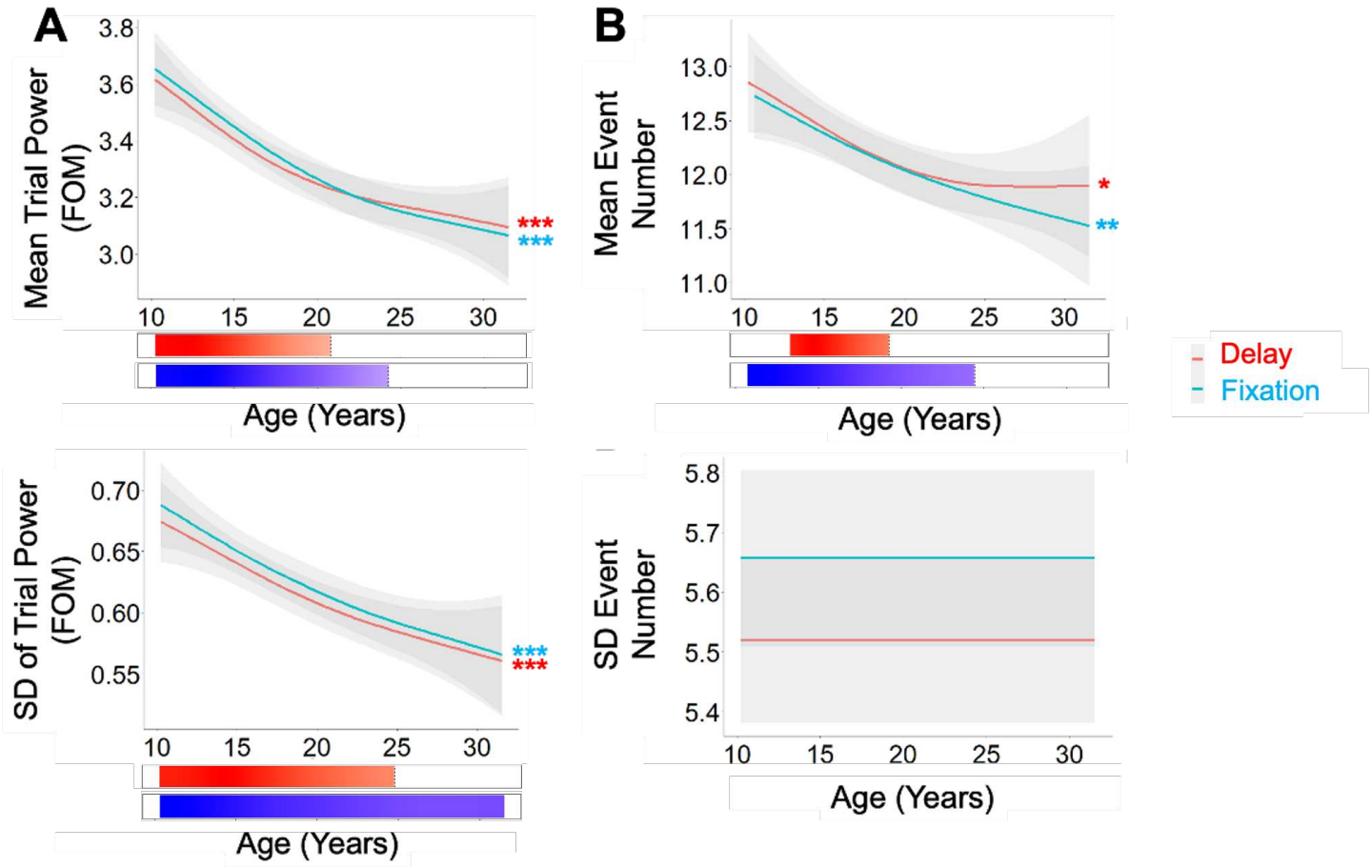

Figure 5. MGS delay period and fixation period before MGS target EEG spectral measures. **A**. Mean trial power of a spectral burst. Growth rates showed significant decreases for 10-21 years of age for mean trial power in the MGS delay period (red bar) and 10-24 years of age for the fixation period (purple bar) **B**. Mean number of spectral bursts per trial. Growth rates showed significant decreases from 13-19 years of age for the delay period (red bar) and 10-24 for the fixation period (purple bar). **C**. Trial-by-trial variability of spectral burst power. Growth rates showed significant decreases for 10-24 years of age for the delay period (red bar) and significant decreases continuing throughout the twenties for the fixation period (purple bar). **D**. Trial-by-trial variability of number of spectral events. No significant growth rates were found. Red and purple bars indicate regions of significant change in delay and fixation periods, respectfully, performance based on the derivative of the GAM model fit. (* p < 0.01; ** p < 0.001; *** p < 0.0001)

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3.3 EEG Spectral Events Association with Behavior

To determine associations between oscillatory bursting activity and age-related improvements in working memory, we compared MGS performance to spectral event measures which showed age-related changes. We found that MGS response latency showed significant decreases (i.e., faster responses) with increasing number of spectral events during the delay period for only adolescents (10-18 years of age) (p = 0.00535; Figure 6). Furthermore, increased trial-by-trial variability in MGS response latency was associated with the trial variability of the number of gamma spectral events, and this was also specific to adolescence (p = 0.00084; Figure 7). No significant associations were found between VGS response latency and the number of spectral events, nor the variability of either measure.

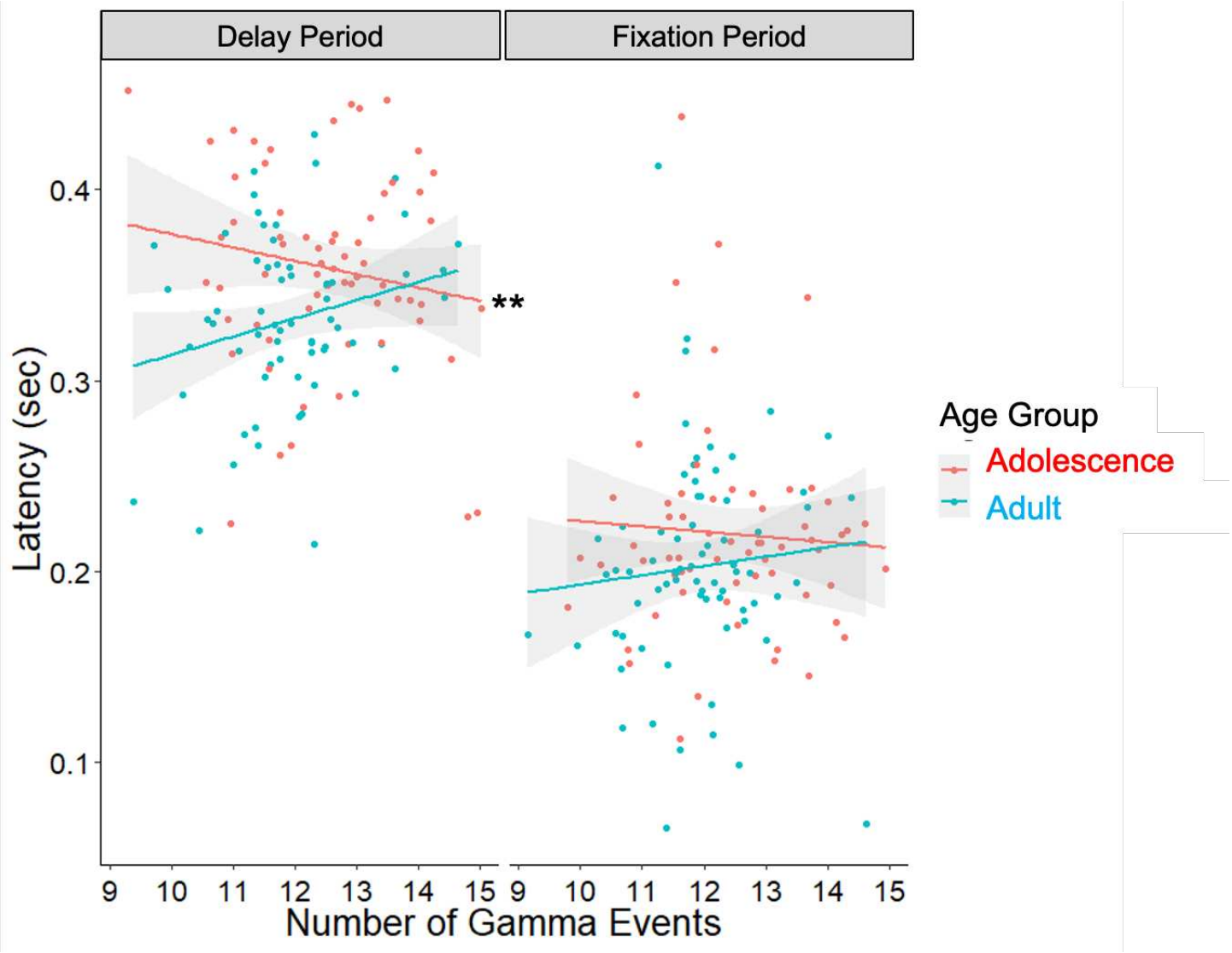

Figure 6. Response latency vs number of spectral events for MGS (left) and VGS (right) for Adolescents 10-18yo (red) and Adults 19-32yo (blue). ** p < 0.001

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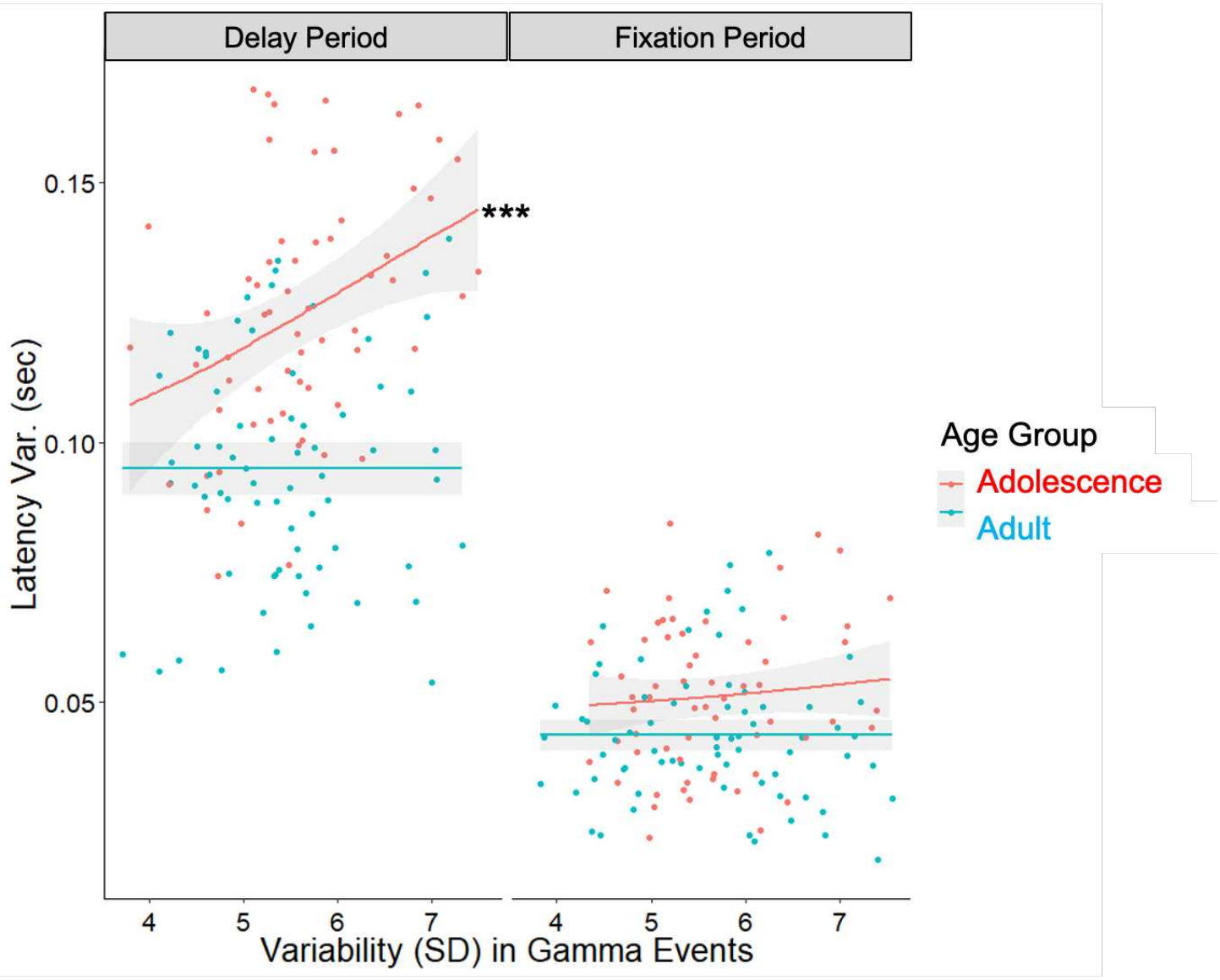

Figure 7. Trial-by-trial variability of response latency vs trial-by-trial variability in number of spectral events for MGS (left) and VGS (right) for Adolescents 10-18yo (red) and Adults 19-32yo (blue). *** $p < 0.0001$

3.4 Discussion

In this study we aimed to understand developmental changes in neural activity that support improvements in working memory through adolescence. Thus, we used EEG since it provides a more direct assessment of neural processing than fMRI, measuring postsynaptic cortical pyramidal cell activity with high temporal resolution that can characterize signal variability across timescales. Specifically, we investigated age-related changes from childhood to adulthood in the spectral events within the gamma frequency band during working memory maintenance and their associations with age-related improvements in working memory performance. We leveraged the power of whole brain EEG data as regional data did not emerge as a predictor of working memory performance and whole brain activity is in accord with the understanding that executive function is supported by a widely distributed circuitry[30,31]. We found that gamma function changed significantly through adolescence in parallel to improvements in working memory with particular associations between gamma dynamics and response latency in adolescence.

Consistent with previous literature[1,2], working memory performance improved into adulthood including increased accuracy and decreases in response latency to make a goal directed response. Importantly, we found significant

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decreases in the average power and number of spectral bursts across adolescence in both the delay and fixation epochs of the task (Figure 5). Furthermore, trial-by-trial variability for event power was found to significantly decrease across adolescence in both task epochs (Figure 5). These results are in agreement with studies showing decreases in power through adolescence across the cortex[21,32–37] with greater reliability in predicting age than MRI measures[38]. Age-related decreases in power are evident in the beta[21], theta[39], and gamma[22] bands with concomitant strengthening of EEG coherence between regions through adolescence[37,40]. Furthermore, previous human EEG studies have characterized elevated gamma frequency power in local field potentials during working memory maintenance[41–44], that decreases across adolescence, suggesting optimization of encoding and maintenance circuitry[23]. These results suggest that basic dynamics of gamma oscillations specialize through adolescence regardless of cognitive demands. Myelination and synaptic pruning across association cortex at this time, and in prefrontal cortex in particular[21,22,36,45,46], may underlie optimization of information processing resulting in decreased need to engage mechanisms supported by gamma oscillations into adulthood.

Age-related gamma changes were not related to working memory accuracy, suggesting that the neural mechanisms supporting the ability to perform an MGS response are present early in development. Basic working memory function is available in infancy[47], and at the trial level, adult level performance is present by childhood, though greater variability across trials results in decreased mean performance[5]. Thus, these results suggest that the core mechanisms of working memory are already available in adolescence. Furthermore, changes in gamma oscillations were associated with response latency and its variability, suggesting that the ability to readily engage executive working memory processes in a consistent fashion continues to improve through adolescence underlying mean improvements in performance. The number of gamma events during the working memory delay was uniquely associated with response latency in adolescents only (10-18 years of age), where a greater number of events was associated with quicker responses. Moreover, increased latency variability was associated with increased event variability in 10–18-year-old adolescents. Importantly, age related changes in gamma events during fixation, which showed a similar change to the delay period, were not associated with performance indicating that these core changes in gamma events come to bear during cognitive demands. Gamma events decreased with age indicating that fewer gamma events result in adult level optimal performance (Figure 5). During adolescence more gamma events provide an advantage to readily generate a working memory response, suggesting that during this time of immaturity more gamma events may be applied as a compensatory mechanism to support a ready response. Finally, increased latency variability was associated with increased event variability but again only in adolescence (Figure 7). Variability in EEG signals has been found to decrease in parallel to developmental decreases in behavioral variability[48]. In contrast, EEG signal complexity and entropy increase with age[49]. Stabilization of neural signaling occurs in parallel to maturation of structural[50] and functional [51–55] connectivity. Thus, decreases in variability may reflect stabilization of neural function and behavior. Variability in gamma events during maturation in adolescence may serve as an adaptive exploratory approach[5], which by adulthood has already reached optimal performance and may be more related to variability in attention. The results we see in adolescence are in accord with neurophysiological data showing that saccade reaction times are strongly correlated with firing activity[56–58], with higher rates of neuronal firing being linked to faster behavioral responses[56,58]. Together, these results suggest that from adolescence to adulthood there may be a process of specialization in which greater neural function may support best performance in adolescence, followed by a shift to less neural function being sufficient for adult level optimal executive function.

We focused on understanding age-related changes in trial level activity as recent evidence indicates its importance for understanding mechanisms underlying working memory delay period dynamics[9,15,16,45,59]. It is traditionally understood that sustained neural activity during working memory delay periods underlie the retention of the information in working memory. However, newer non-human primate evidence suggests that this may be due to the averaging of delay period activity across trials, which misses the transient aspects of neural processes[9]. Consequently, high amplitude rhythmic and low amplitude arrhythmic signal components may get averaged out, resulting in low power in the spectrogram, and uncertainty about the timing and power of specific events[9,60]. The rhythmic power of such events speaks to the magnitude of synchronized activity in membrane potentials within a network, while the duration can infer how long the synchronization is maintained[60]. Sustained and transient events may be driven by different neural mechanisms[60] supporting unique aspects of executive function. Recent work shows compelling evidence that transient bursts during delay periods support maintenance of mnemonic information through the delay period[61]. More specifically, previous work has shown that working memory activity is not stationary, and it has been hypothesized that information is conveyed as

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spiking in short attractor states and held by synaptic changes in-between states[16]. Our findings that trial level gamma activity decreases with development provides compelling new evidence for mechanistic changes in neural processing characterized by refinements in neural function as behavior becomes optimized in adulthood.

Limitations of this study include a cross-sectional cohort and future studies should be done longitudinally to ensure results are replicated in a larger and more diverse sample, as well as to identify developmental changes in both the group and individual levels. Future studies should also investigate region specific developmental changes in EEG and their associations with working memory, as well as the coherence between regions. While we did not find associations in adults with behavior, a more demanding working memory task may elicit associations, as gamma oscillations have been found to be correlated with working memory load[42,62,63].

Together, these results suggest that critical refinements in neural function underlie improvements in working memory from adolescence to adulthood, reflecting the ability to readily and consistently engage mechanisms to employ existing cognitive processes, that during adolescence may leverage increases in neural dynamics and variability to improve performance at the trial level. Characterizing neural mechanisms that underlie normative development can inform impaired trajectories, including psychiatric disorders, where working memory is predominantly affected such as in psychosis[64,65] and depression[66,67], which emerge during the adolescent period[68].

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