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Age predicts peak gamma frequency and N1 amplitude of visual evoked potential

Abdullah Bin Dawood[1*]

Abstract
The current study investigated whether the age of healthy adults could predict the peak gamma frequency and the peak amplitudes of VEP components (N1, P2). 49 healthy participants (aged between 19 and 52 years) underwent EEG recordings during a visual task eliciting clear gamma frequency oscillations and VEP activities. After eliminating noisy and outlier data, data from 41 participants were analysed using simple linear regression. The results indicated that age was a significant predictor of peak gamma frequency and the peak amplitude of VEP-N1 but not the peak amplitude of VEP-P2. Age was negatively associated with peak gamma frequency and the peak amplitude of VEP-N1. These findings support previous research indicating that ageing is associated with decreased cortical inhibition, highlighting the importance of GABA in maintaining cortical E-I balance.

Keywords Excitation-inhibition balance, Peak gamma frequency, Visual evoked potential, VEP, VEP-N1, VEP-P2

Introduction

Cortical excitation and inhibition (E-I) balance is crucial for neural network function [1–3]. Disruption in E-I balance is linked to disorders like epilepsy, Alzheimer's, and autism [4–6]. Ageing affects the cortical E-I ratio, likely due to changes in gamma-aminobutyric acid (GABA) [7, 8]. Older adults have lower GABA + levels in the ventral visual cortex, consistent with declines in the frontal and parietal cortex [8]. GABA + levels rise during adolescence and decline in adulthood, but older adults were found to show higher visual cortex GABA levels, indicating a need for further study [9, 10].

Gamma frequency oscillations, arising from interactions between excitatory neurons and inhibitory interneurons, also assess cortical E-I balance [11]. Positive associations between resting-state GABA in the visual cortex and gamma oscillations have been reported [12, 13]. Age-related changes in peak gamma frequency show inconsistent results. While some studies found a negative association between peak gamma frequency and age [14–16], a positive association between peak gamma frequency and age was also reported [9], highlighting the need for more research on age and gamma frequency.

Age-related changes in visual evoked potentials (VEPs) are thought to reflect cortical E-I balance, as VEP activity sums excitatory and inhibitory postsynaptic potentials [17]. Altering GABA activity affects VEP amplitudes: GABA agonists decrease VEP-N1 and increase VEP-P2, while GABA antagonists have the opposite effect [17–20]. Developmental changes in VEP activity show that N1 amplitude rises with age in children and adolescents. VEP components N1 and P2 amplitudes also increase with age up to 20 years [21]. These findings suggest age-related changes in VEP components but do not align with previous GABA levels and ageing results, possibly due to the different age groups studied [22, 23]. Further research on VEP components in healthy adults is needed.

Utilising a secondary data analysis of only pre-transcranial direct current stimulation (tDCS) data from [24], the

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current study investigated whether age could predict cortical E-I balance changes through peak gamma frequency and VEP components N1 and P2. Based on previous findings on GABA levels and gamma frequency [12, 13]. It hypothesised that age negatively predicts peak gamma frequency and VEP-N1 amplitude but positively predicts VEP-P2 amplitude. However, it was possible that no significant association would be found for peak gamma frequency, as previously reported [16].

Method

Participants

The study included 49 healthy adult volunteers (19 females, 30 males; ages 19–52 years, mean = 26.55, SD = 8.18) from the University of Sheffield. Participants had normal or corrected vision and no history of neurological disorders. Participants received a gift voucher and provided written informed consent. The study received ethical approval from the University of Sheffield's Department of Psychology and followed the Helsinki Declaration.

Electroencephalogram Task

Apparatus

As described previously [24], EEG data was collected in a dimly lit, electrically shielded room using a BioSemi ActiveTwo system with 64 electrodes, placed according to the international 10/10 system. Data was filtered online (0.01–140 Hz) and digitised with BioSemi ActiView software. Electrode impedances were kept below 25 kΩ. Stimuli were displayed on a linearised Viglen LCD monitor (1280 × 1024 pixels, 60 Hz).

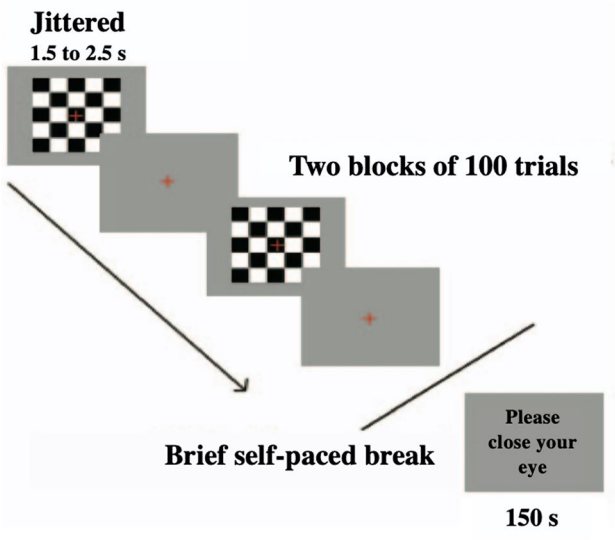

Fig. 1 Illustrates the schematic diagram of the electroencephalogram (EEG). This figure has been reprinted from [35] with permission

Procedures The EEG task, created in MATLAB 2016B [25] with PsychToolbox [26], involved a static checkerboard pattern displayed on a 20-inch LCD monitor. Participants were seated 57 cm from the monitor, fixated on a red dot, while a checkerboard stimulus appeared for an average of 2000 ms with an inter-stimulus interval of 1500–2500 ms, (Fig. 1) Participants were instructed to press the spacebar when the checkerboard disappeared. The task included two blocks of 100 trials each, with a 1–3-minute break between blocks. Participants used their right hand for the first block and left hand for the second. The task lasted 12–15 min, depending on the break duration.

Electroencephalogram Analysis

Independent Component Analysis (ICA) for the time-frequency analysis

The continuous EEG data was sampled online at 2048 Hz using BioSemi ActiView software and down-sampled offline to 512 Hz with BioSemi DBF Decimator software. The data was then analysed offline using EEGLAB and MATLAB scripts. The EEG data was referenced to the vertex electrode (Cz), and a 1 Hz high-pass filter was applied to remove low frequencies. Artifactual segments and channels were visually inspected and removed.

The continuous EEG data for each participant underwent extended ICA (runica) using EEGLAB toolbox (version 14.1.1b) [27] to isolate occipital neural responses to the visual stimulus, and epochs were segmented from 200 ms pre-stimulus to 1,500 ms. ICs were visually inspected for scalp topography, and up to four ICs with focal activity in the occipital cortex were selected for each participant. Time-frequency analysis (wavelet transforms) was performed on the chosen ICs using an in-house MATLAB script. Any ICs with unclear or absent event-related dynamics were removed, and the IC with the clearest event-related dynamics was selected for each participant. Finally, the IC with the clearest sustained visually induced activity in the gamma frequency band (30–90 Hz) was chosen for each participant, (Fig. 2)

The analysis involved wavelet transforms of each participant's selected IC in the time-frequency domain [28]. The complex Morlet wavelet was selected as the function ψ_0 due to its ability to balance time and frequency localisation for feature extraction purposes [29, 30]. The complex Morlet wavelet comprises a complex exponential modulated by a Gaussian, $\omega_0 = 6$, where ω_0 is a nondimensional frequency, as follows:

$$\psi_0(\eta) = \pi^{-1/4} e^{i\omega_0 \eta} e^{-\eta^2/2}$$

The wavelet transform, denoted as $W^x(n, s)$, is is a complex quantity that captures both the power of the time series data (X) and the local phase information, which is localised in both time and frequency (scale)

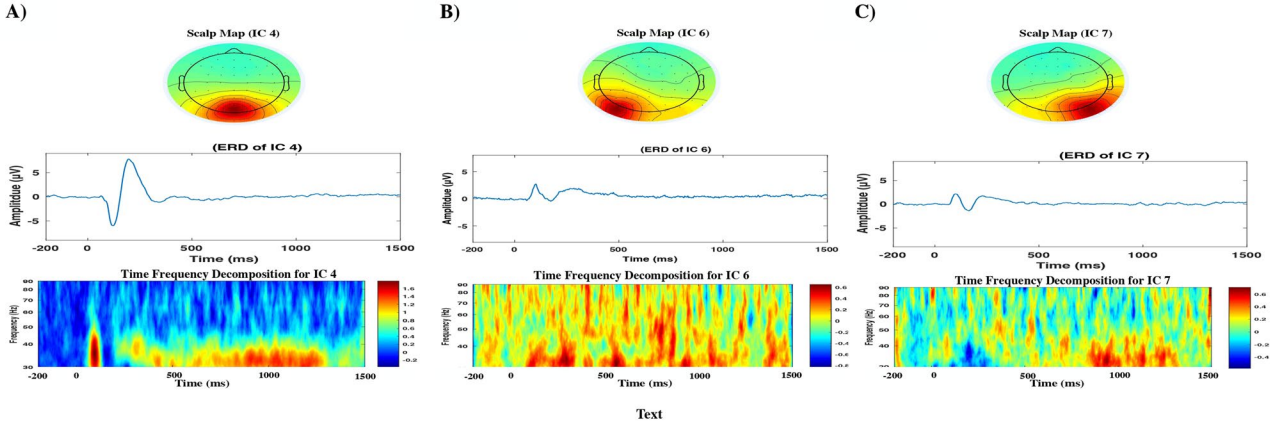

Fig. 2 The ICA components selection for a single participant. **A**, **B**, and **C** represent the scalp map, event-related dynamics, and induced gamma activity of the initially selected components (ICs 4, 6, and 7) based on the visual inspection of scalp tomography of all components. The analyses included the best IC component (i.e., IC 4), which exhibited distinct event-related dynamics and the most apparent induced gamma activity. This figure has been reprinted from [24] with permission

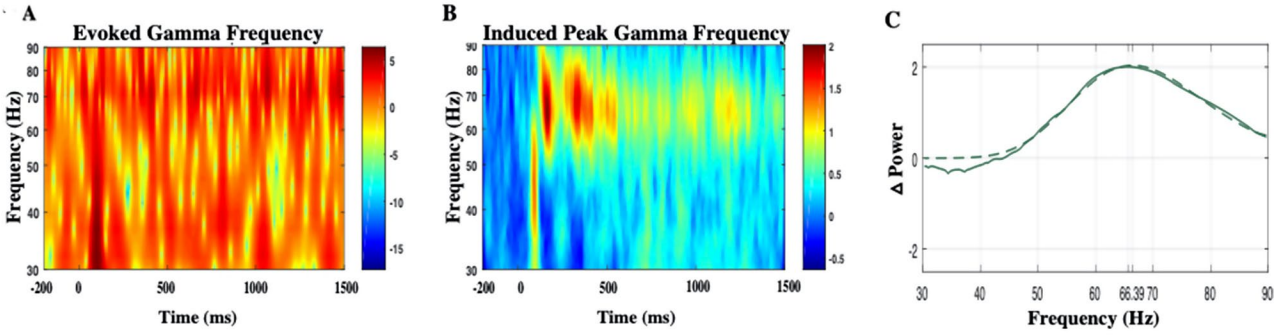

Fig. 3 Illustrates (**A**) evoked gamma frequency, (**B**) induced gamma frequency, and (**C**) power changed at the gamma frequency band of an independent component for a single participant. This figure has been reprinted from [24] with permission

through its modulus and angle, respectively. In this context, (X) refers to the time series data under investigation, while (n) refers to the time index of the individual data points within the series. The scale determines the temporal resolution of the analysis.

The continuous wavelet transform of a time series x_n of N, which is comprised of subsampled data points at equal time intervals of δt [31], is defined as the convolution of x_n with a scaled and translated version of ψ_0:

$$W^x(n,s) = \sqrt{\frac{\delta t}{s}} \sum_{n'-1}^{N} x_{n'} \psi_0^* \left[\frac{(n'-n)\delta t}{s} \right]$$

The wavelet scale was denoted by s and the time index by n. ψ_0^* represented the complex conjugate of ψ_0. The number of octaves for each wavelet scale was set at 1/60. This setting provided optimal spectral resolution in the gamma band range (< 1 Hz) and a smooth picture of wavelet power for our investigation. It is important to note that induced gamma frequency is non-phase-locked to the stimulus onset but is related to it. Induced gamma frequency consists of oscillatory bursts that vary between trials on their onset latency. Thus, averaging trials before performing time-frequency analyses is unlikely to result in observable induced gamma activity, as this type of oscillatory activity is non-phase-locked. Time-frequency analyses were performed for each trial to identify induced peak gamma activity. Then, the power changes were averaged at gamma frequency.

Evoked responses occur around 100 ms after the stimulus onset and are synchronised. The series of single-trial responses can be averaged to detect evoked activity and then analysed using time-frequency analysis, such as wavelet transform. The mean power values for each scale before the stimulus onset were considered baseline and then subtracted from the wavelet transform. The maxima of the resulting matrix provided the maximum increase in evoked power in the gamma frequency band (30–90 Hz) following stimulus presentation (Fig. 3A). To obtain a better estimate of induced gamma activity, the power changes of evoked responses at the gamma frequency band were compared to the induced gamma activity (Fig. 3B), and the peak response was set to time points after cessation of the initial evoked response. A

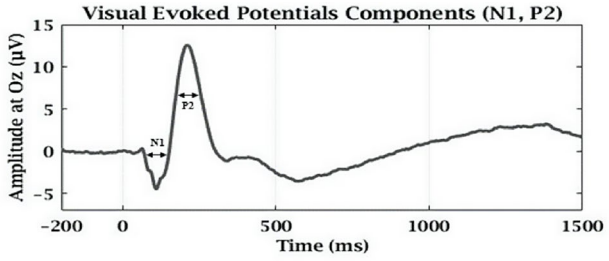

Fig. 4 Illustration of the grand-averaged visual evoked potential (VEP) components N1 and P2

Gaussian non-linear least squares curve was then fitted to the frequency spectra at the time point associated with the maximum gamma power increase following the stimulus presentation. The frequency associated with the maximum point of the fitted curve was considered the metric for each subject's peak gamma frequency (Fig. 3C).

Visual evoked potentials of the Occipital cortex (Oz)

The VEP of the Oz channel was selected for the VEP analysis. After the EEG data were cleaned and epoched from 200 ms pre-stimulus to 1,500 ms post-stimulus, the peak amplitudes of N1 and P2 components were calculated. N1 is the absolute value of the maximum negative amplitude between 80 and 155 ms post-stimulus onset, while P2 is the maximum positive amplitude between 175 and 250 ms post-stimulus onset. A MATLAB script developed in-house was utilised to perform the calculations. The time windows for VEP were chosen based on the participants' grand-averaged VEP waveforms, (Fig. 4)

Results

Eight participants were excluded due to headwear ($N = 2$), medication ($N = 1$), noise and unclear gamma activity ($N = 4$), or significant VEP deviations ($N = 1$). Data from 41 participants (14 females, 27 males; ages 19–52 years, mean = 27.56, SD = 7.79) were analysed.

The average peak gamma frequency was 48.01 Hz (SD = 12.72 Hz). The VEP-N1 component had an average peak amplitude of -6.78 μV (SD = 6.05 μV), while the VEP-P2 component had an average peak amplitude of 13.56 μV (SD = 6.32 μV). Three simple linear regressions were conducted to examine whether age could predict peak gamma frequency and VEP amplitudes (N1, P2). Analyses were done using IBM SPSS version 28 for Windows.

The first linear regression analysis showed that age significantly predicted peak gamma frequency ($F(1, 39) = 6.168$, $p = .017$, $R^2 = 0.137$). Peak gamma frequency decreased by 0.603 Hz per year of age, (Fig. 5.A)

The second analysis found that age significantly predicted VEP-N1 ($F(1, 39) = 4.957$, $p = .032$, $R^2 = 0.113$). VEP-N1 amplitude decreased by 0.261 μV per year of age, (Fig. 5.B)

The third analysis showed that age did not significantly predict VEP-P2 ($F(1, 39) = 0.012$, $p = .914$, $R^2 = 0.003$), (Fig. 5.C).

Further analyses were conducted as previous studies have reported sex-related differences in peak gamma frequency and VEP amplitudes [32, 33]. Three independent sample t-tests assessed sex-related differences in peak gamma frequency and the VEP components (N1, P2).

The results indicated no significant difference in peak gamma frequency between females (M = 47.14, SD = 13.34) and males (M = 48.46, SD = 12.62); $t(39) = -0.313$, $p = .756$. Similarly, no significant difference was found in VEP-N1 between females (M = -7.60, SD = 5.47) and males (M = -6.36, SD = 6.39); $t(39) = -0.619$, $p = .540$. Although females (M = 15.65, SD = 7.58) exhibited slightly higher scores compared to males (M = 12.48, SD = 5.41) in VEP-P2, this difference was not statistically significant; $t(39) = 1.544$, $p = .131$.

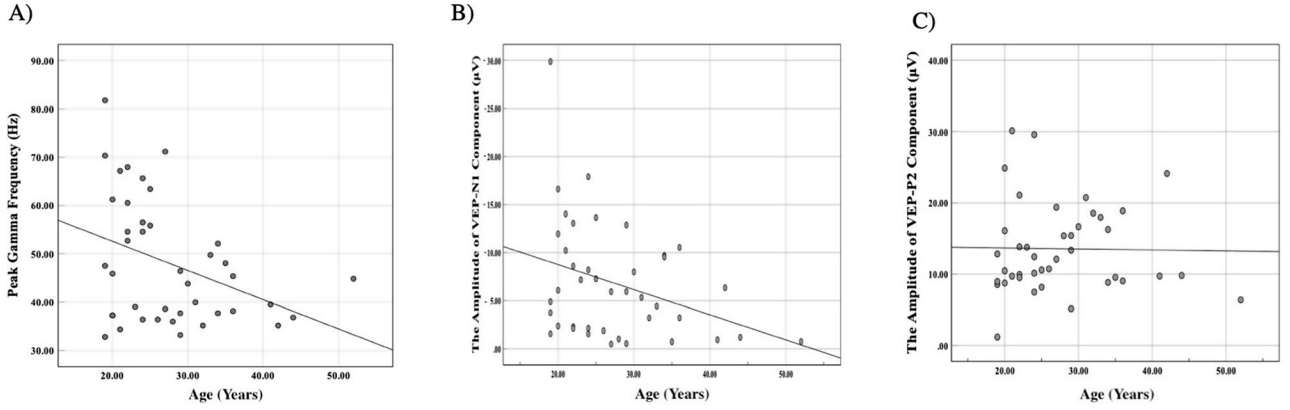

Fig. 5 Prediction of neural activity by participant age. (**A**) Age significantly predicted peak gamma frequency ($p = .017$). (**B**) Age significantly predicted the peak amplitude of the VEP N1 component ($p = .032$). (**C**) Age did not significantly predict the peak amplitude of the VEP P2 component ($p = .914$)

These analyses revealed no significant sex differences in peak gamma frequency and VEP amplitudes (N1, P2). This indicates that sex may not significantly influence these measures, thereby eliminating the need for additional analyses to consider sex as a potential confounding variable.

Discussion

The current study examined whether age could predict peak gamma frequency and VEP components (N1 and P2). Data from 41 participants were analysed using simple linear regressions. Age significantly predicted peak gamma frequency and VEP-N1 amplitude but not VEP-P2 amplitude. Age was negatively associated with peak gamma frequency and VEP-N1 amplitude, suggesting age influences cortical E-I balance.

The current study found an inverse relationship between age and peak gamma frequency, consistent with previous research [14, 16]. This finding indicates an age-related decline in GABA concentration in the visual cortex, as GABA levels are positively associated with peak gamma frequency [12, 13]. Consistently, older adults were found to have lower GABA levels in the visual cortex than younger adults [22].

Additionally, the current study found that age predicted the peak amplitude of VEP-N1, with older age linked to lower VEP-N1 amplitude. This finding is consistent with previous findings showing that VEP-N1 amplitude is negatively associated with GABA concentration [34] and that GABA levels decline with age [22]. The inverse relationship between age and VEP-N1 amplitude aligns with the negative association between age and peak gamma frequency. This finding is notable given the narrow age range of participants (19–52 years) compared to other studies [22].

Inconsistent with previous findings linking GABA levels and VEP-P2 amplitude [17], the current study found that age could not predict the peak amplitude of VEP-P2. While no statistically significant observable association was found between age and VEP-P2 amplitude in adults, age-related changes in the VEP-P2 amplitude have been reported in children and adolescents [21]. As such, VEP-P2 amplitude may be less sensitive to age, requiring a wider age range and larger sample size for detection.

The current study has two main limitations. One limitation is related to the sample size ($N = 41$ participants) with a narrow age range (19–52 years), potentially affecting generalizability. Another limitation is that a single task or technique may not fully capture the relationship between age and cortical E-I balance. Despite these limitations, the current study provided valuable insights. Age was significantly associated with peak gamma frequency and VEP-N1 amplitude, suggesting age influences cortical E-I balance. Future studies should include a broader age range, larger sample size, and multiple tasks to understand this relationship further.

In conclusion, the current study investigated whether age predicts peak gamma frequency and VEP components (N1 and P2). Age was negatively associated with peak gamma frequency and VEP-N1 amplitude but not VEP-P2. This finding may reflect a decline in GABA concentration in the visual cortex. Future research should expand the age range and sample size and use multiple tools to explore the age-cortical E-I balance relationship further.

Abbreviations

E-I	Excitation-Inhibition
EEG	Electroencephalogram
GABA	Gamma-Aminobutyric Acid
Hz	Hertz
ICA	Independent Component Analysis
ICs	Independent Components
LCD	Liquid Crystal Display
MATLAB	Matrix Laboratory
N1	Negative Component 1
P2	Positive Component 2
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
tDCS	Transcranial Direct Current Stimulation
VEP	Visual Evoked Potential
μV	Microvolt

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Author contributions

A. B. confirms sole responsibility for the following: study conception and design, data collection, statistical analysis and interpretation of results, and manuscript preparation.

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Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the University of Sheffield's Department of Psychology Ethics Committee. All participants provided written informed consent before participating in the study.

Consent for publication

Permission was obtained from all participants to use their anonymised data for publication purposes.

Competing interests

The authors declare no competing interests.

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