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Auditory-evoked cortical activity: contribution of brain noise, phase locking, and spectral power

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Abstract

Background—The N1-P2 is an obligatory cortical response that can reflect the representation of spectral and temporal characteristics of an auditory stimulus. Traditionally, mean amplitudes and latencies of the prominent peaks in the averaged response are compared across experimental conditions. Analyses of the peaks in the averaged response only reflect a subset of the data contained within the electroencephalogram (EEG) signal. We used single-trial analyses techniques to identify the contribution of brain noise, neural synchrony, and spectral power to the generation of P2 amplitude and how these variables may change across age group. This information is important for appropriate interpretation of event-related potentials (ERPs) results and in understanding of age-related neural pathologies.

Methods—EEG was measured from 25 younger and 25 older normal hearing adults. Age-related and individual differences in P2 response amplitudes, and variability in brain noise, phase locking value (PLV), and spectral power (4–8 Hz) were assessed from electrode FCz. Model testing and linear regression were used to determine the extent to which brain noise, PLV, and spectral power uniquely predicted P2 amplitudes and varied by age group.

Results—Younger adults had significantly larger P2 amplitudes, PLV, and power compared to older adults. Brain noise did not differ between age groups. The results of regression testing revealed that brain noise and PLV, but not spectral power were unique predictors of P2 amplitudes. Model fit was significantly better in younger than in older adults.

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Conclusions—ERP analyses are intended to provide a better understanding of the underlying neural mechanisms that contribute to individual and group differences in behavior. The current results support that age-related declines in neural synchrony contribute to smaller P2 amplitudes in older normal hearing adults. Based on our results, we discuss potential models in which differences in neural synchrony and brain noise can account for associations with P2 amplitudes and behavior and potentially provide a better explanation of the neural mechanisms that underlie declines in auditory processing and training benefits.

Keywords

aging; auditory; brain noise; cortical-evoked potentials; electroencephalogram (EEG); P2; phase locking; spectral power

Introduction

The obligatory cortical N1-P2 response, measured as a voltage on the scalp, has been used to examine the time course and coincidence of modulations in cortical activity evoked by various experimental manipulations in auditory signals and across groups. The conventional approach is to compare the maximum or mean amplitudes and latencies of the prominent peaks in the averaged evoked response. For experiments with auditory signals, P2 amplitude increases with perceptual ability and auditory learning [1–4], selective attention [5], and hearing loss [6, 7]. Associations between P2 amplitude differences and perceptual abilities, and certain group differences in P2 amplitudes, have fueled interest in this measurement of evoked cortical activity.

Despite the growing interest in N1-P2 peak measurements, a lack of consistency remains in results from electroencephalogram (EEG) studies using auditory signals. For example, previous studies have reported that older adults have larger P2 amplitudes [6, 7], equivalent P2 amplitudes [8–10], and smaller P2 amplitudes, compared to young adults [5, 7, 11]. These discrepancies, and complex interpretations of waveform differences, may result from unique factors in the generation of averaged event-related potentials (ERP). Recorded electrical activity in the EEG primarily reflects summated, slow postsynaptic potentials of cortical neurons [12]. The ERP measured at the scalp may result from a brief synchronous deflection embedded in background activity, a phase resetting of background activity, or some combination of both (Figure 1). Thus, only a small fraction of electrophysiological change elicited by an auditory stimulus may be reflected in the amplitude of the averaged response. Electrical fields summate more strongly across trials if sources are similarly oriented and synchronized, and tend to cancel each other out otherwise. As a result, the amplitude of the averaged response can reflect a combination of noise (i.e., background EEG and artifact), neural synchrony (i.e., phase locking), and spectral power (i.e., peak amplitudes on a trial-by-trial basis). Because these factors can vary systematically between experimental groups, the interpretation of N1-P2 response differences may depend on these sources of variance.

Multiple sources contribute to nonevoked background activity or “noise” in the EEG signal, such as line noise artifacts at multiples of the alternating electrical current. More

importantly, the endogenous background EEG signal or “brain noise” has been studied from baseline periods and during rest and is associated with sensory information processing [13, 14]. Greater variability in brain noise is thought to reflect increased capacity for responding to change and reacting to new stimuli. Early ERPs, such as N1-P2, are thought to be generated primarily by a phase resetting of ongoing activity, or brain noise. As such, stimulus-induced phase resetting results in canceling of noise during baseline periods (when activity is out of phase) and an increase in “signal” following the stimulus. Variability in brain noise is not thought to be random, but instead reflects complex structural changes that impact the functional interactions of distributed neural networks and task performance. Brain noise increases with maturation from infant to adult to an optimum level and correlates positively with task accuracy. Optimal noise in brain networks appears to stabilize behavior and allow for more efficient integration of external stimuli [14]. In older adults, brain noise continues to change and relationships between noise and accuracy are maintained. However, with advanced age, the pattern of changes is not global and brain noise can differ by region, suggesting changes in local dynamics and network communication [14]. This variability across networks and regions may impact ERPs differently depending on experimental manipulations and acquisition techniques. Moreover, variability in brain noise may explain inconsistent results among studies, with some showing similar noise levels for younger and older adults and others reporting increased noise levels for older adults [15]. Brain noise may also change with disease or damage. For example, increased levels of brain noise in individuals with schizophrenia may disrupt information processing [16]. Taken together, these results suggest that brain noise as captured in ongoing EEG activity contributes to neural signaling (reviewed in Ref. [14]) and behavior, and evolves with age [14, 15] and disease state [16].

Noise is typically calculated by measuring the variation in the EEG signal during a prestimulus period across trials [15]. However, this same time period preceding the stimulus is also used to normalize the ERP response and calculate peak amplitudes because prestimulus activity is typically assumed to have a minimal impact on stimulus-locked responses. Although not stimulus locked, the assumption of task independence remains to be confirmed by examining the effect of variations in brain noise on peak amplitudes and behavior.

As shown in Figure 1, in addition to the amount and variation of brain noise, neural synchrony, or phase locking, largely impacts ERP peak amplitudes, either in the form of phase resetting of brain noise or in the phase consistency of induced activity across trials. As such, an alternative to the peak amplitude metric is phase locking value (PLV), or the consistency of phase across trials at a given frequency. An important advantage of PLV is that it is independent of differences in baseline levels of noise and signal power. In addition, given that it is a measure of neural synchrony, PLV may provide a human parallel to phase locking measures acquired in single-unit auditory neurophysiological measures in laboratory animals [17] or simulated with predictions from physiologically inspired auditory-nerve computational models [18]. Indeed, declines in PLV may be associated with declines in speech recognition or other tasks that require accurate neural timing mechanisms [19]. To date, most investigations that included PLVs and ERPs focused on associations at the level of the brainstem and sustained potentials, such as the frequency-following response [17, 20–

22]. Individual differences in the PLV at the level of the brainstem vary with perceptual ability across several tasks, are positively correlated with response magnitude in younger adults, and vary across the lifespan [17, 20–22]. Given that phase locking is fundamental to the generation of an averaged ERP at any level of the auditory system, measurement and analysis of PLV may explain differences in amplitudes of cortical ERP responses, such as the P2.

Another source of variance that contributes to the amplitude of the ERP is spectral power. Due to the timing of the N1-P2 response (150–250 ms), the peak of spectral power occurs in the 3–8 Hz range, as expected ($1/0.25\text{ s} = 4\text{ Hz}$). Unlike the time-domain averaged ERP response, estimates of spectral power include both induced and endogenous, or nonphase locked, activity relative to a predetermined baseline. Similar to peak amplitude measurements, power estimates are susceptible to differences in the noise floor, including artifacts and brain noise that occur within the same frequency range as the response to the stimulus. Spectral power and PLV are expected to be closely related, as both are dependent on extracting the component of the measured response that is consistent across individual trials. However, certain pathologies may more likely disrupt phase synchrony or power estimates; as such, the inclusion of both measures may contribute to appropriate interpretation of differences across experimental groups.

In this article, we present a subset of findings that revealed decreases in P2 amplitudes in older adults as compared to younger adults acquired in response to a silent gap, or the offset of broadband noise [5], and new analyses of noise, PLV, and spectral power, with the goal of determining how these factors contribute to individual and age-related differences in P2 amplitudes. Understanding the complex interactions of brain noise, phase locking, and spectral power and their effects on the widely used and reported peak amplitude, is important for appropriate interpretation of ERP signals for individuals and groups and an improved understanding of age-related auditory system neural pathologies. Although the present findings explore how these relationships change with age, and are elicited by an offset response and focus on the P2 response, the mechanisms explored are influential in the generation of all ERPs and may vary widely across different experimental groups.

Materials and methods

A subset of the data reported in Harris et al. [5] was re-analyzed to assess the contribution of brain noise, phase locking, and signal power to P2 amplitudes in this large sample of younger and older adults. Additional details of participants, stimuli, and procedures are provided by Harris et al. [5].

Participants

Participants included two groups of adults: younger [$n = 25$; mean age = 24.19 (3.42) years; 17 females] and older [$n = 25$; mean age = 69.82 (7.11) years; 17 females]. All participants had normal hearing (defined as thresholds $\leq 25\text{ dB HL}$ at 250, 500, 1000, 2000, 3000, and 4000 Hz). Participants provided written informed consent before participating in this MUSC Institutional Review Board approved study.

Data acquisition and analysis

The stimuli consisted of a broadband noise, low-pass filtered at 5 kHz, presented continuously, with silent gaps of 3, 6, 9, 12, or 15 ms distributed every 2–2.2 s (Figure 2). Each gap duration was presented sequentially 250 times, followed by the next gap duration. The order of presentation was randomized across listening conditions and participants. Each subject exhibited a robust N1-P2 response at the 15-ms gap duration (the focus of the current analysis). Stimuli were digitally created using Tucker Davis Technologies (TDT) system 3 hardware (Alachua, FL, USA) and presented monaurally to the right ear through a TDH-39 headphone at an overall level of 80 dB SPL. Participants were instructed to ignore the stimulus and read quietly. Electrophysiological (EEG) signals were recorded with a 64-channel Neuroscan Quickcap™ based on the international 10–20 system and connected to a SynAmpsRT (Compumedics Neuroscan, Charlotte, NC, USA) [A/D rate = 1000 Hz, bandpass filtered 0.1–200 Hz]. Bipolar electrodes were placed on the skin above and below the left eye for recording vertical electro-oculogram activity. Offline, raw EEG recordings were subjected to an automatic artifact rejection algorithm. Some 250 trials were collected; trials contaminated by excessive peak-to-peak deflections ($\pm 150 \mu\text{V}$) at the channels not adjacent to the eyes were automatically rejected. On average, 17 trials were rejected per subject. The number of trials rejected did not vary between younger and older subjects. For each individual, ocular artifacts were corrected by means of independent component analyses. P2 peak amplitude was measured using SCAN version 4.4 acquisition software (Compumedics Neuroscan, Charlotte, NC, USA). Individual trials were segmented into epochs surrounding the onset of the gap (–100 to 1000 ms). Epochs were baseline corrected (–100 to 0 ms) and bandpass filtered from 1 to 30 Hz. For each participant, average waveforms (ERPs) were computed relative to gap onset. Based on group average waveforms, P2 was defined as the largest positivity following N1 occurring between 130 and 220 ms, relative to baseline.

For the current analysis of brain noise, PLV, and spectral power, data were re-epoched offline from –1000 to 2000 ms time-locked to the onset of the gap. Brain noise was assessed during a prestimulus baseline period (–400 to –200 ms) [14]. Brain noise was estimated using Matlab (Mathworks, USA) as the standard deviation (SD) of the signal during the –400 to –200 ms preonset time window (in 1-ms steps), pooled across trials (~ 250 trials) [15] under the assumption that physiologically noisier signals are more variable during the prestimulus interval. Individuals with noise greater than 2.5 SD from the group were excluded; based on this criterion, results from 1 younger and 1 older adult were excluded from further analysis, leaving 48 subjects in the dataset. Time-frequency analysis was performed to estimate power and PLV using a continuous Morlet wavelet transform as implemented in EEGLab (<http://sccn.ucsd.edu/eeglab/>), using linear-spaced frequencies from 2 to 30 Hz in 2-Hz steps [23, 24]. The time-frequency window of interest was defined a priori as a stimulus-locked period from 50 to 250 ms and focused on theta (4–8 Hz) frequencies, where peak amplitude and PLV were strongest. PLV is unitless and represents a continuous measure across individual trials, ranging from perfect phase locking (PLV = 1) to phase independence (PLV = 0). Power estimates in each time-frequency bin were transformed to estimates of relative power change in dB units compared with power

estimates in a baseline window (–500 to –300 ms pregap onset). The new analysis was limited to electrode FCz where the P2 peak amplitude was the largest.

Age group differences between younger and older adults were assessed using independent sample t-tests. Associations among variables were assessed using Pearson correlation coefficients to determine the extent to which brain noise, PLVs, and power predicted P2 amplitudes. Multiple regression analyses were performed to assess interaction effects and relative significance of variables in predicting P2 amplitudes. All analyses were performed in *R* statistics software (version 3.0.3, R Project for Statistical Computing, <http://www.r-project.org/>) to determine whether the fit of the linear model significantly decreased after removing interaction and main effects; variables were excluded from the linear model when they did not significantly affect the model fit. For all analyses, p-values of < 0.05 were considered statistically significant.

Results

As described earlier, brain noise, PLV, and spectral power were estimated based on EEG recordings from younger and older adults with normal hearing to characterize their independent contributions to variability and group differences observed in ERP P2 peak amplitudes. As reported previously, older adults had significantly smaller P2 amplitudes than younger adults ($t = 4.56$, $p < 0.001$). New estimates and analyses of PLV and spectral power now reveal significantly lower PLVs ($t = 5.47$, $p < 0.001$) and reduced power ($t = 6.27$, $p < 0.001$) for older than younger adults. For younger adults mean PLV was 0.51 (SD = 0.13), and mean power was 1.78 (SD = 0.89). For older adults mean PLV was 0.31 (SD = 0.12) and mean power was 0.50 (SD = 0.40). In contrast, brain noise levels were not significantly different between younger adults (mean = 2.50, SD = 1.05) and older adults (mean = 2.11, SD = 1.09) ($t = 1.19$, $p = 0.24$). As shown in Figure 2(B–D), all three variables, i.e., noise, PLV, and power were positively correlated with P2 amplitudes ($0.42 < r < 0.71$, $p < 0.004$).

We used linear regression and model testing to determine the extent to which noise, PLV, and power uniquely contributed to P2 amplitude and to identify interactions with age. Model testing showed that the power $\times$ age interaction, and main effect of power did not contribute to model fit ($F < 0.91$, $p > 0.35$), and were subsequently removed from the model. All remaining interactions (age $\times$ noise, age $\times$ PLV) significantly improved the model fit ($F > 11.96$, $p < 0.001$). To test whether noise and PLV were significant predictors of P2 amplitudes in both younger and older adults, separate regression analyses were performed for each subsample. Results of these analyses are provided in Table 1. Noise and PLV significantly contributed to variation in P2 amplitudes in younger and older adults. Fisher z -transformed correlation coefficients from each model (younger and older) were compared, and demonstrated that model fit for younger adults was significantly better than for older adults ($z = 2.1$, $p = 0.02$). The linear regression model results show that the variation in noise and PLV, but not power, are unique predictors of P2 amplitudes in both younger and older adults (Figure 2E,F), but these relationships may not be stable across age groups.

Discussion

The goal of the current study was to identify the contribution of brain noise, neural synchrony, and spectral power to ERP peak amplitudes. We demonstrated that neural synchrony and brain noise were unique predictors of P2 amplitudes, while power was not. The strong association between phase locking and P2 amplitudes, but not power, may be related to ERP generation in the current study, which was triggered by the offset of the noise (onset of the gap). Detection of a brief silent gap in an ongoing noise is dependent on temporal resolution and neural synchrony to accurately encode the offset of the stimulus. Unlike the offset of a sound, the onset of a new stimulus may elicit an ERP either through phase resetting or the induction of new neural activity, resulting in increased power. Although our results support the phase-resetting hypothesis and suggest that age-related decreases in the amplitude of P2 are the result of decreases in neural synchrony, additional studies are needed to explore how these variables interact across different experimental populations and paradigms.

Auditory ERPs can reflect neural mechanisms that underlie differences in behavior and are sensitive to group differences including those that relate to age, hearing loss, presence of tinnitus, and brain plasticity associated with auditory training. With regard to aging, various neurobiological factors account for differences in ERP potentials across the lifespan, such as skull thickness, synaptic density, myelination, and changes in excitation/inhibition [25, 26]. Results of the previous studies, including Harris et al. [5], have provided evidence that reduced P2 amplitudes may result from temporal jitter, declines in neural synchrony, and/or neuronal loss or disintegration of synaptic connectivity in auditory cortices [7, 27]. These new results support many of our earlier hypotheses and provide additional evidence that declines in neural synchrony contribute to smaller P2 amplitudes in older adults. Neural synchrony is dependent on the integrity of white matter and myelin in the cortex. Age-related declines in neural synchrony are consistent with declines in white matter integrity observed throughout the cortex (reviewed in Refs. [28–31]). In contrast to the decrement in P2 amplitudes observed in the current study, several studies have reported increased P2 amplitudes associated with auditory training and musical experience [1, 2, 4, 32]. We hypothesize that these enhanced ERP amplitudes may be the result of increased myelination or white matter in auditory cortex and subsequent increased neural synchrony. Consistent with this premise, structural imaging studies have demonstrated increased white matter and myelin with training [33–35]. These changes in white matter microstructure may help explain why enhancements appear to generalize to other stimuli exposed to but not necessarily learned [32, 36].

Previous studies have suggested that brain noise may evolve during development to some optimum level [14], and subsequent increases or decreases may arise from some pathological conditions that are reflected in brain noise and compromise task performance. These results suggest an intriguing possibility that certain brain dysfunctions may produce noise patterns that can be distinguished from the normal range. Our current study demonstrated reduced P2 amplitudes in a large sample of older adults with normal hearing compared to younger adults, but observed similar levels of brain noise across age groups. In contrast to our sample of older adults, previous studies have observed increased ERP

amplitudes in adults with hearing loss [6, 37], tinnitus [38], and even long-term cochlear implant users [39]. Similar increased levels of activity are observed in animal models of hearing loss [39] and tinnitus [40, 41]. We hypothesize that increased P2 amplitudes associated with hearing loss and tinnitus reflect increased brain noise, which may also impede efficient integration of external stimuli.

In summary, we examined the contribution of individual and age-related differences in brain noise, neural synchrony, and spectral power to demonstrate the influence of these underlying factors in widely reported P2 peak amplitudes. Our results suggest that declines in neural synchrony and individual differences in brain noise explain a large portion of the variance in ERP response amplitudes. This information may also explain how increased P2 amplitudes can be associated with both improved and declining task performance and can further our understanding of the underlying neural mechanisms associated with declines in auditory processing and brain plasticity associated with auditory training and experience.

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Figure 1.

Simulated EEG activity.

Standard event-related potential (ERP) models (A–C) include a phase reset (A), pure ERP (B), or average of both for each trial (C). During each simulation trial with the phase-reset model, a sinusoid with a frequency between 4 and 16 Hz restarted its oscillation at 150 ms (A) or at a variable time 150 ± 70 ms (D). For each simulated trial, the pure ERP model generated background noise based on the human ERP spectrum; then added a negative peak at 150 ms (B) or 150 ± 70 ms (E). Root-mean-square power and peak-to-noise ratios were equalized across models so that for each trial, the mixture model could be produced by averaging the phase-reset and pure ERP model. In each plot, black lines show individual simulated trials and red lines depict the average ERP from 500 simulations. Regardless of the model, the mean peak amplitude decreases in relation to poor neural response timing or poor phase locking, by varying the onset of responses or phase-reset timing by up to 70 ms (D–F). Each EEG simulation was implemented using the code adapted from Yeung et al. (2004; 2007), which is available online from the authors (<http://www.cs.bris.ac.uk/~rafal/phasereset>).

Figure 2.

Associations between P2 amplitude, brain noise, phase locking value, and spectral power. (A) Group average waveforms for younger adults (black, mean = 1.62 μ V, standard deviation–SD = 1.27) and older adults (red, mean = 0.41 μ V, SD = 0.34) elicited by a 15-ms silent gap measured from electrode FCz. (B–D) Scatter plot showing P2 amplitudes vs. brain noise (mean SD), PLV, and theta power in younger adults (black) and older adults (red). Brain noise, PLV, and theta power were significantly correlated with P2 amplitudes in younger and older adults. (E,F) Scatter plots showing results of linear regression analyses (Table 1) for younger and older adults. The y-axis represents the mean standardized residual P2 amplitude value after controlling for the remaining variables, in (E) the y-axis represents P2 amplitudes after controlling for PLV and power, in (D) after controlling for brain noise, and power, and in (F) after controlling for brain noise and PLV. Brain noise and PLV remained significantly associated with the standardized residual P2 amplitudes, whereas power did not.

Table 1

Linear regression model results for younger and older adults.

	Estimate	t-Score	p-Value
Younger adults (n = 24)			
Brain noise (SD)	0.63	5.19	< 0.001
PLV	6.81	7.23	< 0.001
Multiple $R^2 = 0.77$, $p < 0.001$			
Older adults (n = 24)			
Brain noise (SD)	0.17	2.97	0.007
PLV	1.63	3.22	0.004
Multiple $R^2 = 0.52$, $p = 0.001$			