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Altered temporal dynamics of neural adaptation in the aging human auditory cortex

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ABSTRACT

Neural response adaptation plays an important role in perception and cognition. Here, we used electroencephalography to investigate how aging affects the temporal dynamics of neural adaptation in human auditory cortex. Younger (18–31 years) and older (51–70 years) normal hearing adults listened to tone sequences with varying onset-to-onset intervals. Our results show long-lasting neural adaptation such that the response to a particular tone is a nonlinear function of the extended temporal history of sound events. Most important, aging is associated with multiple changes in auditory cortex; older adults exhibit larger and less variable response magnitudes, a larger dynamic response range, and a reduced sensitivity to temporal context. Computational modeling suggests that reduced adaptation recovery times underlie these changes in the aging auditory cortex and that the extended temporal stimulation has less influence on the neural response to the current sound in older compared with younger individuals. Our human electroencephalography results critically narrow the gap to animal electrophysiology work suggesting a compensatory release from cortical inhibition accompanying hearing loss and aging.

1. Introduction

Neural adaptation is an important feature for any perceptual system and refers to a reduction of the neural response magnitude due to stimulus repetition (Herrmann et al., 2014; Jääskeläinen et al., 2007). Adaptation of neural responses might provide the basis for detecting relevant—and filtering out irrelevant—environmental information (Escera and Malmierca, 2014; Jääskeläinen et al., 2007; Nelken, 2014), for segregating two auditory streams (Micheyl et al., 2005, 2007), and for providing perceptual constancy across different contexts (Clifford et al., 2007).

In human auditory electroencephalography (EEG), neural adaptation is commonly investigated by measuring the auditory cortex N1 response (Hari et al., 1982; Herrmann et al., 2014; Näätänen and Picton, 1987) or the P2 response (Hari et al., 1982; Herrmann et al., 2013a; Lanting et al., 2013). The N1 and P2 responses to a repeated sound decrease when the interval between first and second sound presentations is shorter because neurons have less time to recover from adaptation (Davis et al., 1966; Hari et al., 1982; Picton et al., 1978; Sams et al., 1993). Based on studies using temporally isochronous sound stimulation, the N1 magnitude is thought to depend only on the directly preceding time interval (Budd et al., 1998; Lü et al., 1992; Mäkelä et al., 1993; McEvoy et al., 1997; Rosburg et al., 2006; Sams et al., 1993; Zhang et al., 2011). However, single-neuron responses in animals appear to adapt gradually within tone sequences (Duque and Malmierca, 2015; Gutfreund, 2012) and a few N1 studies in young, normal hearing human adults using more variable sequences (in contrast to long isochronous stimulation) suggest long-lasting adaptation across multiple tone presentations (Okamoto and Kakigi, 2014; Papanicolaou et al., 1985b; Zacharias et al., 2012; but see also; Roth et al., 1976). Studies on P2 adaptation are less common, sometimes showing response pattern comparable with N1 responses (Hari et al., 1982; Herrmann et al., 2013a; Picton et al., 1978), whereas other times differences between N1 and P2 responses have been emphasized (Roth et al., 1976; for a review on the P2 see; Crowley and Colrain, 2004).

Neural response adaptation is not a static phenomenon across the lifespan. Neural adaptation as measured using the N1 response is fully developed early in life (Ruhnau et al., 2011), but previous

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studies suggest that neural adaptation is impaired in older adults such that neural populations exhibit longer times to recover from adaptation (Kisley et al., 2005; Papanicolaou et al., 1984). However, this is in contrast to research in animals suggesting that aging and noise exposure are associated with reduced neural inhibition and augmented response magnitudes along the ascending auditory pathway (Caspary et al., 2008; Hughes et al., 2010; Llano et al., 2012; Popelár et al., 1987; Stolzberg et al., 2012; Takesian et al., 2012), as well as the observation of increased response magnitudes for older humans in fast stimulus presentation designs (Bidelman et al., 2014; Herrmann et al., 2013b). More generally, human EEG studies investigating cortical responses in aging have provided mixed results. Some studies have revealed larger N1 responses for older compared with younger adults (Amenedo and Díaz, 1999; Bidelman et al., 2014; Herrmann et al., 2013b; Sörös et al., 2009; Tremblay et al., 2003), some report smaller responses (Harris et al., 2008; Papanicolaou et al., 1984), whereas others observed no difference (Bennett et al., 2004; Czigler et al., 1992; Ford et al., 1979; Woods, 1992). Furthermore, frequency-specific adaptation (i.e., the reduction of neural responses by preceding sounds with different frequencies) seems to be unaltered in older adults (Herrmann et al., 2013b). Yet, hearing loss and aging most strongly affect temporal processing abilities (Anderson et al., 2012; Barsz et al., 2002; Mamo et al., 2016; Pichora-Fuller, 2003; Walton, 2010). Hence, it may be the temporal-coding properties rather than frequency-coding properties of neurons in auditory cortex that may be affected in older people. We hypothesized that age-related changes in temporal coding would correlate with the extent to which neural adaptation depends on the temporal context of auditory stimulation. We further hypothesized that increased N1 response magnitudes accompanying aging might be related to altered temporal dynamics of neural adaptation.

The present EEG study provides a detailed examination of the temporal dynamics of human auditory response adaptation in different temporal contexts (regular, irregular) in younger and older adults: (1) we tested for long-lasting response adaptation beyond the interval between two successive sounds; (2) we predicted that human aging would be accompanied by changes in cortical response adaptation that are consistent with the reduced cortical inhibition observed in animals (Caspary et al., 2008). Simulations from a single-neuron model incorporating neural adaptation closely matched our empirical observations in scalp recordings (Brette and Gerstner, 2005).

2. Materials and methods

2.1. Participants

Twenty-one younger (mean age, 24.6 years; range, 18–31 years; 11 females) and 18 older (mean age, 61.7 years; range, 51–70 years; 10 females) healthy German-speaking adults participated in the experiment. Note that older adults in the present study were slightly younger than in some previous human aging studies (Alain et al., 2012; Bennett et al., 2004; Bidelman et al., 2014; Leung et al., 2013; but see also; Czigler et al., 1992). Three additional participants took part in the study (one younger, two older) but were excluded due to technical problems during recording (N = 2) or due to >30% of data being contaminated by artifacts (N = 1). Participants did not report any neurological diseases or any hearing problems. They gave written informed consent before the experiment and were paid 7 Euros per hour for their participation. The study was conducted in accordance with the Declaration of Helsinki and cleared by the local ethics committee of the University of Leipzig.

Age groups did not differ in self-reported musical ability or experience ($t_{36} = 0.22$, $p = 0.828$, $r = 0.037$; assessed using a rating scale ranging from 0 to 10). Furthermore, age groups did not differ in self-reported spatial hearing abilities ($t_{37} = 1.40$, $p = 0.170$, $r = 0.224$) or quality of hearing ($t_{37} = 1.16$, $p = 0.254$, $r = 0.187$), but differed in self-reported speech comprehension ($t_{37} = 2.68$, $p = 0.011$, $r = 0.403$) as measured by a short German version of the Speech, Spatial, and Qualities of Hearing Scale (Gatehouse and Noble, 2004). Older participants reported slightly lower speech comprehension abilities than younger participants (younger, 7.92 ± 1.20; older, 6.71 ± 1.62; mean and standard deviation [SD]; scale ranged from 0 to 10, where 10 reflects perfect speech comprehension abilities).

For each participant, an audiogram was acquired for each ear at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. All participants except one showed normal hearing at 1000 Hz for both ears (i.e., ≤25-dB hearing level [HL]; Wayne and Johnsrude, 2015; 1000 Hz was the stimulation frequency used in the present study; Fig. 1A). For one older participant, HL was at 30 dB for the worse ear. We refrained from excluding this participant's data from the analyses because sound level was adjusted for each participant individually, and the statistical results reported below do not qualitatively change by inclusion or exclusion (for a similar procedure see Bidelman et al., 2014).

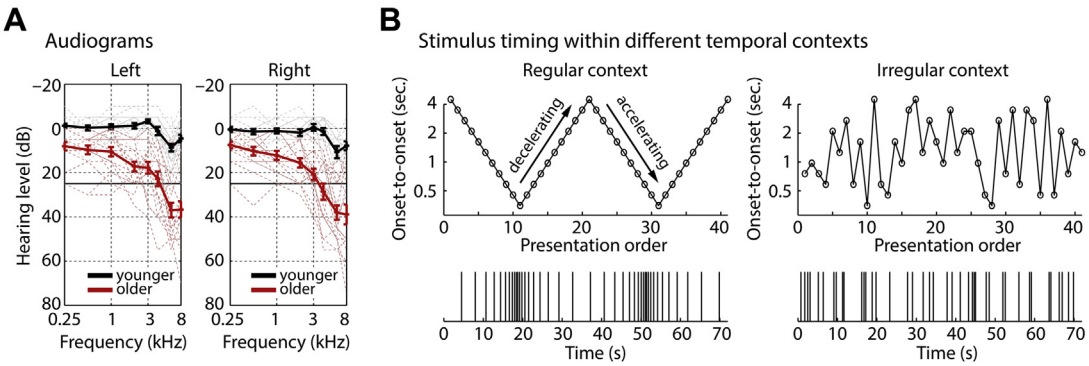

Fig. 1. Audiometric data and stimulation design. (A) Audiograms (mean across participants) for left and right ears for each participant group (younger in black, older in red; thin dashed lines show individuals). The error bars reflect the standard error of the mean (SEM). The black horizontal line at 25 dB marks the normal-hearing boundary. (B) Two temporal contexts (regular, irregular) containing identical numbers of tones and identical distributions of onset-to-onset intervals preceding tones. Top: onset-to-onset intervals as a function of presentation order (y-axis is logarithmically spaced). Bottom: tones (indicated by vertical lines) as a function of time (in seconds). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.2. Acoustic stimulation and procedure

Before the EEG recording, each participant's hearing threshold was determined for the 1000-Hz stimulation frequency using the method of limits (Leek, 2011). For the EEG recordings, acoustic stimulation consisted of 1000-Hz pure tones (100 ms duration, including 0.007 seconds rise and fall times) presented at 55 dB above a participant's individual hearing threshold (sensation level; for similar a procedure see Kisley et al., 2005). Tones were presented in two temporal contexts with different temporal structure: regular versus irregular. In the regular temporal context, tone presentation continuously alternated between accelerating and decelerating. In detail, 19 20-tone trains were continuously presented, and tones within each train were separated by logarithmically changing onset-to-onset intervals (N = 20 onset-to-onset intervals for one cycle/train: 4.5, 3.486, 2.7, 2.092, 1.62, 1.255, 0.972, 0.753, 0.583, 0.452, 0.35, 0.452, 0.583, 0.753, 0.972, 1.255, 1.62, 2.092, 2.7, 3.486 seconds, for accelerating to decelerating; see Fig. 1B). The duration of the preceding onset-to-onset interval served as the independent variable by which trials were sorted into conditions.

For the temporally irregular context, tones and the corresponding onset-to-onset intervals that preceded tones were randomized separately for each of the 19 trains within a sequence. As a consequence, the identical number of tones was presented in regular and irregular temporal contexts (19 trains × 20 intervals = 380 tones; + one additional tone at the beginning of each sequence to establish the first onset-to-onset interval), and both temporal contexts were based on identical distributions of onset-to-onset intervals (albeit expressing different temporal structure). Hence, if only the interval duration directly preceding a tone affected the neural response magnitude, no response differences between temporal contexts would be expected.

Presentation of each temporal context was repeated three times creating six different blocks (two temporal contexts × three repetitions). Blocks were separated by short pauses, the order of blocks (temporal contexts) alternated between regular and irregular, and the starting block was counterbalanced across participants. Throughout the experiment, 57 trials per onset-to-onset interval were presented in both the regular and irregular temporal contexts.

2.3. EEG recording and preprocessing

Participants sat in a comfortable chair in a sound-attenuated and electrically-shielded booth while their electroencephalogram was recorded. They watched a silent movie (with subtitles) of their choice and were instructed to ignore the acoustic stimulation. EEG was recorded from 26 Ag/Ag-Cl scalp electrodes (Easycap), left and right mastoids, nose (online reference), and ground (at the sternum). The sampling rate was 500 Hz (TMS international amplifier; 135 Hz low-pass filter; impedances <5 kΩ).

Offline data analysis was carried out using MATLAB software (MathWorks, Inc.). Raw data were filtered with an 80-Hz low-pass finite impulse response filter (FIR, 42 points, Hamming window) and a 1.2-Hz high-pass FIR filter (697 points, Hann window). The high-pass filter was specifically designed for strong DC (>120 dB) and drift suppression which would allow omission of baseline correction (Herrmann et al., 2014; Maess et al., 2007). Nevertheless, all data reported here were baseline corrected (for details see in the following) because different age groups might differ in overall activity. Note that all results reported in the following were qualitatively similar when baseline correction was omitted.

Data were divided into epochs ranging from −1.8 to 1.8 seconds time-locked to tone onset. Independent components analysis (ICA; runica method, Makeig et al., 1996; logistic infomax algorithm, Bell and Sejnowski, 1995) was computed using Fieldtrip software (version 20130727; Oostenveld et al., 2011). Components containing artifacts such as blinks, heart- or muscle-related activity, or noisy channels were rejected, and the data were then projected back to the original electrodes. ICA reduces artifacts in EEG recordings and is thus advantageous for the overall data quality and the number of data points (trials) that can be submitted to further analysis. Note also that a spatial ICA as performed here does not affect the phase of EEG signals (Henry et al., 2014). The number of components rejected did not differ between age groups (Wilcoxon rank sum test: $p = 0.206$; median number of components rejected in each group was ten). After ICA, epochs containing a signal range larger than 120 μV in any of the electrodes were excluded. The number of trials rejected did not differ between age groups (Wilcoxon rank sum test: $p = 0.724$; median number of trials rejected semi-interquartile range [sIQR]: younger = 7 [11.5], older = 8.5 [7.5]). Finally, epochs were filtered with a 30-Hz low-pass FIR filter (113 points, Blackman window), cut to range from −0.07 to 0.35 seconds for data analysis, and the mean activity within the −0.07 to 0 seconds time window was subtracted from the epoch (baseline correction).

2.4. Data analysis: responses to tones in regular versus irregular temporal contexts

Response time courses for each of the 11 unique onset-to-onset intervals (0.35, 0.452, 0.583, 0.753, 0.972, 1.255, 1.62, 2.092, 2.7, 3.486, 4.5 seconds) were obtained as follows. Separately for temporally regular and for temporally irregular sequences, single-trial time courses for a unique onset-to-onset interval and its direct neighbors (i.e., shorter and longer intervals) were binned and averaged (Ingham and McAlpine, 2005). For example, to obtain the average response for the 1.255-s interval, we averaged all trials for the 0.972-s, 1.255-s, and 1.620-s (n−1, n, n+1) onset-to-onset intervals (end points only had one neighbor). The overlap across intervals was used to increase the number of trials in the response average, thereby increasing the signal-to-noise ratio, while ensuring that the onset-to-onset intervals remained controlled across temporal contexts (regular, irregular).

The analyses focused on N1 and P2 amplitudes for which neural adaptation has been reported previously (Briley and Krumbholz, 2013; Herrmann et al., 2014; Lanting et al., 2013; Sams et al., 1993) but which might differ in their adaptation properties (Roth et al., 1976). To this end, mean amplitudes for a frontocentral electrode cluster (Fz, F3, F4, Fc3, Fc4, Cz, C3, C4) were extracted separately for the N1 time window (0.8−0.11 seconds) and the P2 time window (0.14−0.26 seconds). As in previous studies (Herrmann et al., 2013a; Ruhnau et al., 2011), we here chose the average across an electrode cluster rather than focusing our analysis on an individual electrode (e.g., Cz) to improve the signal-to-noise-ratio and to reduce the potential impact of noise and subject variability. (Note that the current statistical results are qualitatively unaffected by using an electrode cluster versus an individual electrode, e.g., Cz, with the former being even more conservative).

A measure of dynamic response range was calculated as the difference between the maximum and the minimum amplitude across onset-to-onset intervals separately for each temporal context (i.e., the minimum N1 [or P2] amplitude value across the 11 unique onset-to-onset intervals was subtracted from the maximum N1 [or P2] amplitude value across the 11 unique onset-to-onset intervals). Note that in the present study this approach yields qualitatively similar results (and the same conclusions) compared with fitting a linear or higher-order polynomial function to the amplitude data (e.g., N1 or P2) as a function of onset-to-onset-interval and statistically analyzing the estimated linear or higher-order coefficients (e.g., comparing the linear coefficients

between temporal contexts and age groups). We chose to calculate the max–min amplitude difference to examine response modulations as a function of onset-to-onset interval instead of function fits because the former is the simpler measure and leads to the same conclusions.

Separately for N1 and P2 time windows, an analysis of variance (ANOVA) including the within-subject factor context (regular, irregular) and the between-subject factor age group (younger, older) was calculated using the dynamic response range (difference between maximum and minimum amplitude) as the dependent measure. Effect sizes for ANOVAs are reported as partial eta-squared (η^2_p). Effect sizes for potential follow-up *t*-tests are reported as $r_{equivalent}$ (Rosenthal and Rubin, 2003; hereafter referred to simply as *r*), which is equivalent to a Pearson product-moment correlation for two continuous variables and to the square root of partial η^2 for ANOVAs.

2.5. Data analysis: responses to tones within accelerating versus decelerating segments

Single trials within the temporally regular context were separated into an "accelerating" context (4.5 seconds–0.35 seconds) and a "decelerating" context (0.35 seconds–4.5 seconds). Single-trial time courses for a unique onset-to-onset interval and its direct neighbors (i.e., shorter and longer intervals) were binned and averaged (Ingham and McAlpine, 2005). Responses were averaged across the frontocentral electrode cluster and analyses focused on N1 and P2 amplitudes.

Specifically, we focused on two measures. First, the dynamic response range was calculated as the difference between the maximum and the minimum amplitude across onset-to-onset intervals separately for accelerating and for decelerating segments (similar to the procedure described previously; excluding the 0.35 and 4.5 seconds intervals because they were nonunique to the different segments). Separately for N1 and P2 time windows, an ANOVA including the within-subject factor context (accelerating, decelerating) and the between-subject factor age group (younger, older) was calculated. Second, the mean amplitude across onset-to-onset intervals was calculated separately for tones presented in the accelerating and decelerating segments (excluding the 0.35 and 4.5 seconds intervals). Separately for N1 and P2 time windows, an ANOVA including the within-subject factor context (accelerating, decelerating) and the between-subject factor age group (younger, older) was calculated.

2.6. Adaptive exponential integrate-and-fire model to explain N1 effects

Recovery from neural adaptation in EEG and magnetoencephalography experiments is commonly assessed by fitting an exponential function to neural response amplitudes (commonly to the N1) as a function of preceding interval duration (Lü et al., 1992; Mäkelä et al., 1993; McEvoy et al., 1997; Sams et al., 1993). The time constant of the exponential function describes the time over which recovery from adaptation occurs. However, the exponential function fit assumes a static recovery function that is reset at sound onset (or offset; with neural activity being zero at full adaptation), whereas the current N1 data show that responses are not only affected by the immediately preceding interval duration (see in the following) but also by the extended temporal history of sound presentations. A more recent approach combined two exponential functions and a neuron pool to allow for more flexibility (Zacharias et al., 2012). However, this model failed to explain some of the temporal context and aging effects reported below.

Here, we made use of an adaptive exponential integrate-and-fire model (aEIF; Brette and Gerstner, 2005) to qualitatively capture our N1 data. The aEIF model is a single-neuron model that incorporates long-lasting adaptation. It has been extensively studied and used to describe empirical data in previous reports (Cohen, 2014; Deemyad et al., 2012; Hildebrandt et al., 2015; Jolivet et al., 2008; Naud et al., 2008; Walcott et al., 2011). It is described by the following two equations:

$$C\frac{dV}{dt} = -g_L(V - E_L) + g_L\Delta_T\, exp\left(\frac{V - V_T}{\Delta_T}\right) - w + I$$

$$\tau_w\frac{dw}{dt} = a(V - E_L) - w$$

where *V* is the membrane potential, *w* is an adaptation variable, and *I* a synaptic current (input). These variables change over time, whereas the other parameters are constants (listed in Table 1).

The membrane potential *V* and the adaptation variable *w* are affected by the synaptic current *I*. The synaptic current consisted of Gaussian noise (μ = 0 nA, σ = 0.1 nA; simulating random subthreshold membrane potential fluctuations) over time to which a 0.1-s long current (duration of tone stimulation) of 0.4 nA was added at stimulation times. At spike time, *V* is set to the peak potential of 20 mV and subsequently reset to −50 mV (reset potential). Furthermore, *b* is added to *w* at spike time and reflects the spike-triggered adaptation (Brette and Gerstner, 2005). The critical parameter of the model is the adaptation time constant (τ_w), which determines how fast the neuron recovers from adaptation over time.

Simulation of spiking activity was carried out for both temporal contexts (regular, irregular; Fig. 1B) and age groups. For each tone condition (onset-to-onset interval) and temporal context, the mean firing rate was calculated for the 0- to 0.15-s time window. We collapsed across a broad time window here because we did not expect a direct correspondence between the EEG N1 time window and the spiking activity from the single-neuron model. The EEG field potential reflects slow postsynaptic potential fluctuations and might thus capture the integration of spiking activity over a longer time period. Most important, spiking activity and field potentials are functionally related (albeit reflecting different phenomena; Bullock, 1997; Buzsáki et al., 2012; Logothetis and Wandell, 2004; Logothetis et al., 2001), thus motivating the exploration of whether single-neuron spiking activity can qualitatively capture modulations in EEG responses.

Model parameters were manually but systematically varied to qualitatively capture the empirical N1 temporal-context and aging effects. We did not quantitatively fit the single-neuron spiking activity to EEG responses because the quantitative relation between a single-neuron model and EEG signals is unknown, due to extensive computational time (Rossant et al., 2010) and because we aimed to

Table 1
Parameters and parameter values of the adaptive exponential integrate-and-fire model used in the present study

Parameter	Value
C (membrane conductance), nF	0.45
g_L (leak conductance), nS	12
E_L (leak reversal potential), mV	−67
V_T (spike threshold), mV	−52
Δ_T (slope factor), mV	2
τ_w (adaptation time constant), s	10, 6[a]
a (subthreshold adaptation), nS	4
b (spike-triggered adaptation), nA	0.004
dt (increment of time), s	0.0005

[a] τ_w was 10 s for younger and 6 s for older participants.

explore the qualitative relation between an electrophysiologically motived model and EEG responses without claiming a one-to-one match between the microscopic versus macroscopic signals.

3. Results

3.1. Responses to tones within regular versus irregular temporal contexts

Fig. 2A depicts response time courses for tones presented in regular and irregular temporal contexts, separately for younger and older participants. Multiple time courses are displayed reflecting responses to tones preceded by different interval durations. N1 and P2 amplitudes were clearly modulated by interval duration within the 0.8–0.11 seconds and 0.14–0.26 seconds time windows, respectively.

To test for overall amplitude differences between contexts, responses were averaged across all trials separately for each temporal context. For N1 amplitudes, an ANOVA (within-subject, context; between-subject, age group) revealed slightly larger overall amplitudes for irregular than regular contexts ($F_{1,37} = 4.54$, $p = 0.040$, $\eta^2_p = 0.109$) and larger amplitudes for older than younger listeners ($F_{1,37} = 18.22$, $p < 0.001$, $\eta^2_p = 0.330$). The interaction was not significant ($F_{1,37} = 0.11$, $p = 0.746$, $\eta^2_p = 0.003$). For the P2, amplitudes were larger for irregular than regular contexts ($F_{1,37} = 27.57$, $p < 0.001$, $\eta^2_p = 0.427$). There was no effect of age group ($F_{1,37} = 0.15$, $p = 0.705$, $\eta^2_p = 0.004$) and no interaction ($F_{1,37} = 1.87$, $p = 0.180$, $\eta^2_p = 0.048$).

Next, the dynamic response range, the degree to which neural response magnitude is altered due to preceding interval duration, was calculated as the difference between the maximum and the minimum amplitude across interval durations (Fig. 2B and C). The difference scores were subjected to an ANOVA. For N1 amplitudes, a main effect of context ($F_{1,37} = 34.03$, $p < 0.001$, $\eta^2_p = 0.479$) and a main effect of age group ($F_{1,37} = 4.82$, $p = 0.034$, $\eta^2_p = 0.115$) were observed. The dynamic response range (i.e., modulation of N1 amplitude) was larger for regular than irregular contexts, indicating that N1 amplitude depends on the temporal context in which stimuli are presented and not only on the directly preceding temporal interval (in which case we would have expected no difference between contexts). The dynamic response range was also larger for older than for younger participants (Fig. 2B). The interaction was not significant ($F_{1,37} = 0.30$, $p = 0.589$, $\eta^2_p = 0.008$). For P2 amplitudes, main effects of context ($F_{1,37} = 8.45$, $p = 0.006$, $\eta^2_p = 0.186$; regular > irregular) and age group ($F_{1,37} = 5.68$, $p = 0.023$, $\eta^2_p = 0.133$; younger > older) were again observed, this time qualified by an context × age group interaction ($F_{1,37} = 17.65$, $p < 0.001$, $\eta^2_p = 0.323$). The dynamic response range was larger in the regular than in the irregular context for younger ($t_{20} = 4.83$, $p < 0.001$, $r = 0.734$) but not for older participants ($t_{17} = 0.99$, $p = 0.336$, $r = 0.233$; Fig. 2C).

Thus far, we have analyzed neural responses to tones preceded by the identical interval duration but that were presented in the different temporal contexts. The reduction in dynamic response range for irregular compared with regular temporal contexts (Fig. 2B) shows that the N1 response magnitude is influenced by the extended temporal history of sound stimuli beyond the directly preceding interval.

The next analysis investigated whether an effect of temporal context (regular vs. irregular) is observed when an extended

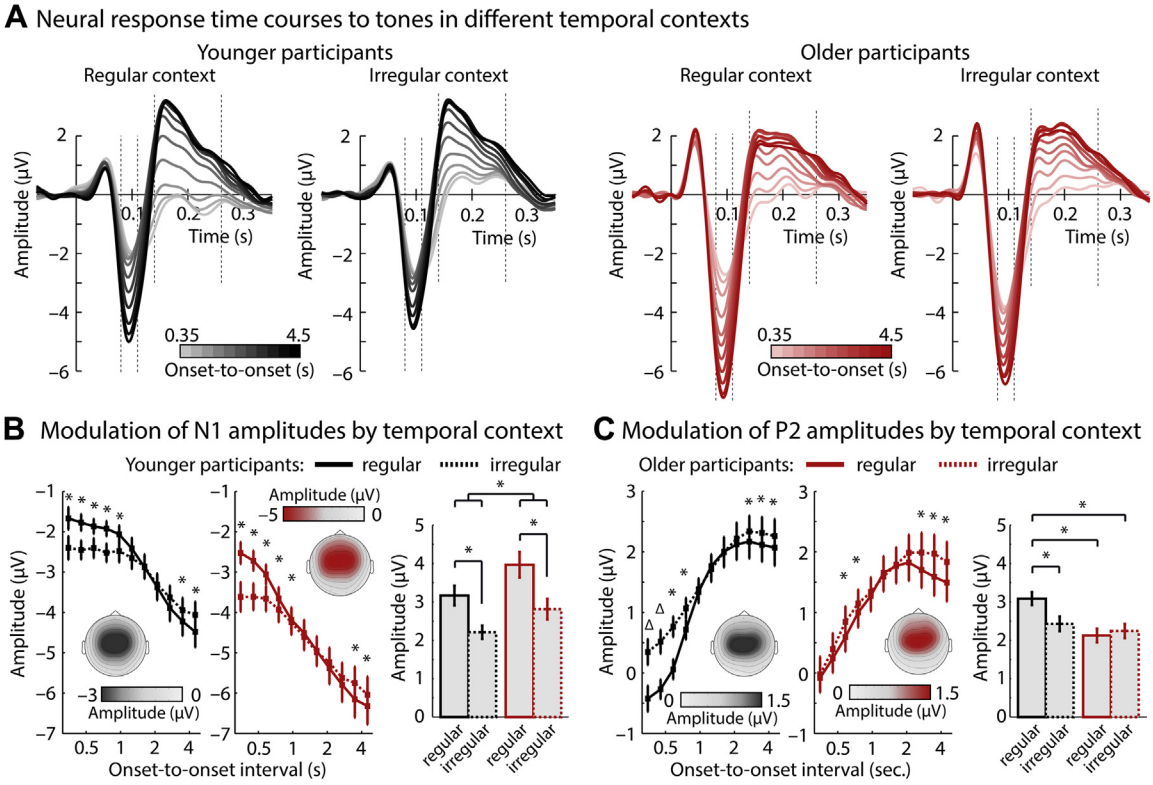

Fig. 2. Neural responses in different temporal contexts. (A) Response time courses for regular and irregular contexts and for younger and older participants (average across frontocentral electrode cluster). Different lines reflect neural responses to tones preceded by different intervals. Dashed vertical lines mark the two time intervals of interest: N1 (0.08–0.11 seconds) and P2 (0.14–0.26 seconds). (B and C) Left: N1/P2 amplitudes as a function of onset-to-onset interval. For the figure only, an exploratory ANOVA (within-subject factor, context; between-subject factor, age group) on N1/P2 amplitudes was independently conducted for each onset-to-onset interval. *indicates a significant main effect of context ($p < 0.05$) without an interaction with age group; Δ–indicates a significant context × age group interaction ($p < 0.05$). Right: bar graphs show the dynamic response range, that is, the difference between the maximum and minimum amplitude across onset-to-onset intervals. For the N1 response range, both main effects were significant ($p < 0.05$) without an interaction. For the P2 response range, the context × age group interaction was significant ($p < 0.05$). Abbreviation: ANOVA, analysis of variance.

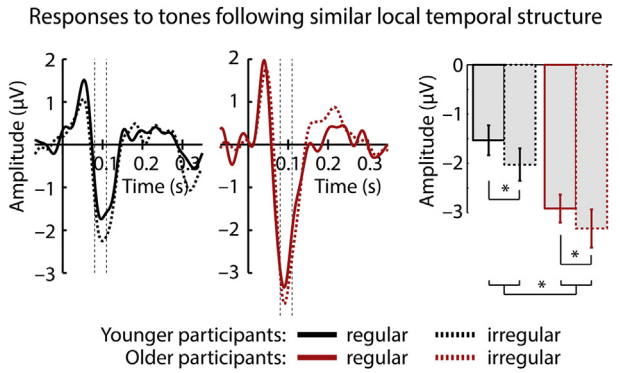

Fig. 3. Responses to tones after similar local temporal structure in different temporal contexts. Responses to tones directly preceded by short intervals (0.35, 0.452, and 0.583 seconds) and matched local temporal structure (i.e., the temporal pattern of the preceding three tones) between irregular and regular temporal contexts. N1 amplitudes show main effects of context and age group ($^*p < 0.05$) but no interaction.

temporal sequence pattern is similar in both contexts. In detail, responses to tones directly preceded by short intervals (0.35, 0.452, and 0.583 seconds) were extracted such that the extended local temporal structure (i.e., the temporal pattern of three successive tones) was matched between irregular and regular temporal contexts. The response to the last of the three tones was analyzed. The analysis focused on the three shortest intervals (0.35, 0.452, and 0.583 seconds) because N1 amplitude differences between contexts were particularly pronounced at short intervals (larger responses for tones in irregular than regular contexts; Fig. 2B, left). Furthermore, three tones were chosen because that was the maximum for which we were able find the identical local sequence patterns in the regular and irregular temporal contexts while still having a sufficient number of trials for the analysis. Here again, N1 amplitudes were larger in the irregular than regular temporal context ($F_{1,37} = 4.35$, $p = 0.044$, $\eta^2_p = 0.105$; ANOVA with within-subject factor context and between-subject factor age group), and larger for older compared with younger adults ($F_{1,37} = 10.71$, $p = 0.002$, $\eta^2_p = 0.225$; Fig. 3). The interaction was not significant ($F_{1,37} = 0.04$, $p = 0.834$, $\eta^2_p = 0.001$). These results show that the response to a sound is influenced by the temporal stimulation history up to at least three preceding sound presentations.

3.2. Responses to tones within accelerating and decelerating segments

Tones presented in the regular context were separated into those presented during accelerating versus decelerating segments and neural responses were examined as a function of preceding interval duration (Fig. 4A). We focused on two measures: First, the dynamic response range was calculated as the difference between the maximum and the minimum amplitude across interval durations (as mentioned previously). Second, the mean amplitude across onset-to-onset intervals was calculated for tones within accelerating segments and within decelerating segments of the regular context.

For the N1 time window, the dynamic response range was not different between responses in accelerating versus decelerating segments ($F_{1,37} = 0.29$, $p = 0.596$, $\eta^2_p = 0.008$) but was slightly larger in older compared with younger participants ($F_{1,37} = 3.88$, $p = 0.056$, $\eta^2_p = 0.095$; Fig. 4B left). No interaction between context and age group was observed ($F_{1,37} = 0.73$, $p = 0.397$, $\eta^2_p = 0.019$). The mean N1 amplitude (average across onset-to-onset intervals) for tones in accelerating segments was significantly larger than for tones in decelerating segments ($F_{1,37} = 123.97$, $p < 0.001$, $\eta^2_p = 0.770$; Fig. 4B right), and responses were larger for older than younger listeners ($F_{1,37} = 19.76$, $p < 0.001$, $\eta^2_p = 0.348$). Critically, the difference between accelerating and decelerating was larger for younger compared with older participants as indicated by the context × age group interaction ($F_{1,37} = 5.49$, $p = 0.025$, $\eta^2_p = 0.129$). Hence, although older participants have a larger dynamic response range, their responses are less modulated by temporal context (accelerating versus decelerating).

In contrast, for P2 amplitudes, the dynamic response range was larger in the decelerating compared with the accelerating parts of the sequence ($F_{1,37} = 61.42$, $p < 0.001$, $\eta^2_p = 0.624$) and generally smaller for older than for younger participants ($F_{1,37} = 11.38$, $p = 0.002$, $\eta^2_p = 0.235$). No interaction between context and age group was found ($F_{1,37} = 0.53$, $p = 0.471$, $\eta^2_p = 0.014$). In addition, there was no difference in the mean P2 amplitude (average across onset-to-onset intervals) between responses to tones in

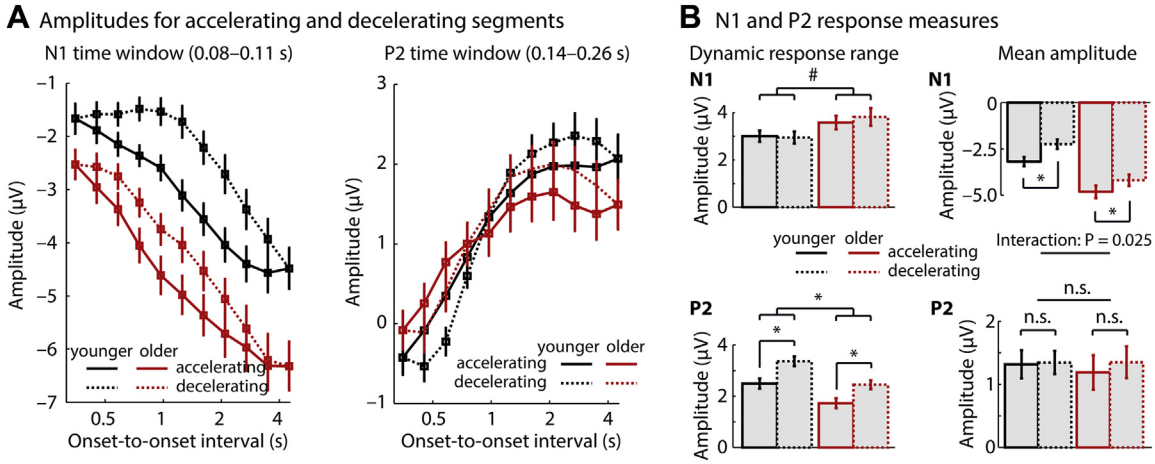

Fig. 4. Neural responses to tones in accelerating and decelerating segments of the regular context. (A) N1 and P2 amplitudes as a function of onset-to-onset interval. Responses are shown separately for accelerating (solid line) and decelerating (dashed line) segments as well as for younger (black) and older participants (red). (B) N1 (top row) and P2 (bottom row) response measures. The left column shows the dynamic response range (maximum−minimum response). The right column shows the mean amplitudes (across intervals) for tones in accelerating and decelerating segments. $^*p < 0.05$, $\#p < 0.10$. Abbreviation: n.s., not significant. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

accelerating versus decelerating contexts ($F_{1,37} = 2.17$, $p = 0.149$, $\eta^2_p = 0.055$), no difference between age groups ($F_{1,37} = 0.04$, $p = 0.850$, $\eta^2_p < 0.001$), and no context × age group interaction ($F_{1,37} = 1.05$, $p = 0.312$, $\eta^2_p = 0.028$). Hence, the neural response pattern in accelerating versus decelerating contexts was substantially different for the N1 and the P2 time windows.

3.3. Distribution of N1 single-trial responses: response magnitude and response variability

Next, we were interested in the variability of the N1 amplitudes as previous work suggests that aging might be related to more stereotyped responses (Garrett et al., 2011, 2013). We focused on in the accelerating and decelerating segments contrast for which we observed age-related changes (see previous section). In detail, we calculated for each condition the proportion of trials that elicited an amplitude greater than unique criterion amplitudes (range, −40 to 40 μV, 300 steps; i.e., the proportion of trials having an amplitude greater than, e.g., −40 μV and so forth; Fig. 5A). A logistic function was fitted to the proportion data as a function of criterion amplitude separately for tones with different preceding intervals and separately for accelerating and decelerating segments. Two measures were extracted from the logistic function fits: the intercept reflecting the mean N1 amplitude and the sIQR reflecting N1 amplitude variability.

First, we confirmed the results depicted in Fig. 4, by showing that the mean intercept (N1 amplitude) was larger for older than younger listeners ($F_{1,37} = 18.42$, $p < 0.001$, $\eta^2_p = 0.332$), that the intercept differed between accelerating and decelerating contexts (main effect of context: $F_{1,37} = 114.83$, $p < 0.001$, $\eta^2_p = 0.756$), and that this difference is larger in younger than older adults (context × age group interaction: $F_{1,37} = 3.88$, $p = 0.057$, $\eta^2_p = 0.095$; when only the Cz electrode is considered: $F_{1,37} = 6.85$, $p = 0.013$, $\eta^2_p = 0.156$; Fig. 5B and C top). Second, we asked whether response variability (sIQR) depended on temporal context (accelerating, decelerating), but no difference between accelerating and decelerating segments was found ($F_{1,37} = 0.02$, $p = 0.885$, $\eta^2_p < 0.001$). However, the overall response variability (sIQR) was reduced in older compared with younger participants ($F_{1,37} = 5.51$, $p = 0.024$, $\eta^2_p = 0.130$; Fig. 5B and C bottom). There was no context × age group interaction ($F_{1,37} = 0.01$, $p = 0.916$, $\eta^2_p < 0.001$).

In Fig. 5A, the N1 amplitude difference between age groups is reflected in the overall left shift (intercept) and the N1 age group difference in response variability is reflected in the steeper slope (sIQR) of the fitted logistic functions for older compared with younger participants. Indeed, the inspection of Fig. 5A shows that younger adults have more low-amplitude trials than older adults. We tested whether the N1 amplitudes differed between age groups for the 10% of trials with the lowest amplitudes and for the 10% of trials with the largest amplitudes. We observed larger N1 amplitudes for older than younger participants for low-amplitude trials (proportion of trials < 0.1; $t_{37} = 4.53$, $p < 0.001$, $r = 0.598$), whereas this N1 amplitude difference was absent for trials eliciting large responses (proportion of trials > 0.9; $t_{37} = 0.01$, $p = 0.995$, $r = 0.001$). Hence, response magnitudes in older participants were particularly enhanced for low-response magnitude trials.

3.4. Ruling out other contributions to age effects on overall N1 amplitude

The previous analyses showed that older, compared with younger, participants have larger N1 amplitudes (in particular for trials with low-response magnitude) and less variability in their response amplitudes. However, overall N1 amplitudes reflect the average across multiple trials. As a consequence, a difference in overall N1 amplitude between age groups could be due to intertrial differences in response timing rather than a true amplitude difference. Assuming differences in single-trial response time variability between age groups, we would expect that the averaged N1 response deflections would differ in width (e.g., wider deflection when single-trial response timing is variable). We selected trials such that N1 amplitudes after trial averaging were matched between age groups (younger, −3.75 μV ± 1.38 SD; older, −3.79 μV ± 1.22 SD; $t_{37} = 0.09$, $p = 0.931$, $r = 0.014$). Then, for each participant, the N1 peak latency was estimated, and a quadratic function was fitted to amplitudes as a function of time (centered on the peak latency; Nourski et al., 2015; there was no significant difference in N1 peak latency between age groups: $t_{37} = 1.55$, $p = 0.129$,

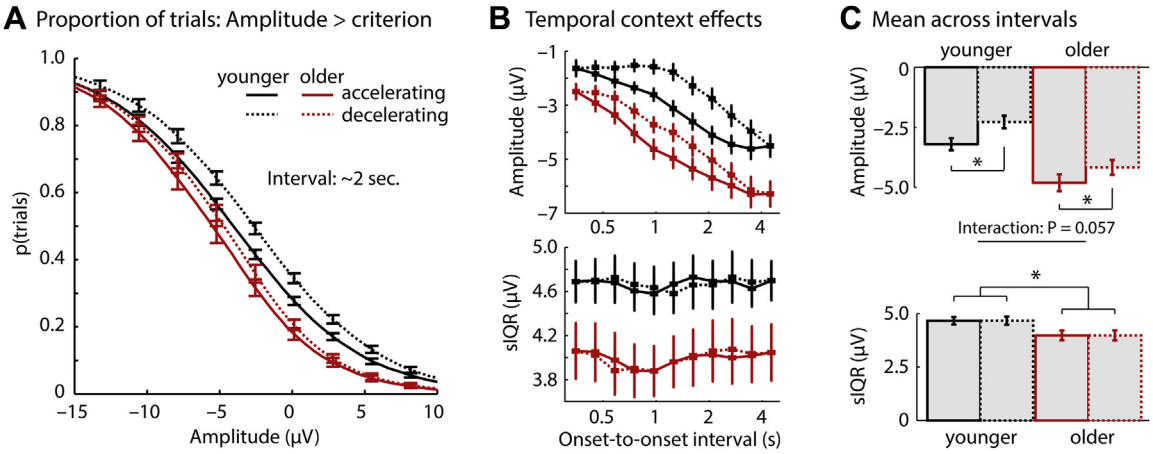

Fig. 5. Description of the full distribution of N1 single-trial responses. (A) Proportion of trials that elicited an amplitude larger than unique criterion amplitude values on the x-axis. Proportion of trials is shown for the onset-to-onset interval of 2.092 seconds. Error bars (SEM) are shown for a subset of the 300 data points. A logistic function is fitted to the proportion data. Two dependent measures were extracted: Intercept reflecting the amplitude value on the x-axis corresponding to 0.5 proportion of trials; sIQR reflecting half the difference between the amplitude values corresponding to 0.75 and 0.25 proportion of trials. (B) Top: estimated intercept from logistic function fit for N1 amplitudes as a function of onset-to-onset interval. The estimated intercept is equivalent to the mean amplitude. Bottom: sIQR calculated from logistic function fit for N1 amplitudes as a function of onset-to-onset interval. sIQR is a measure of response variability. (C) Top: mean amplitude (intercept) across onset-to-onset intervals for accelerating and decelerating segments. Bottom: mean sIQR across different onset-to-onset intervals for accelerating and decelerating segments. *$p < 0.05$. Abbreviations: SEM, standard error of the mean; sIQR, semi-interquartile range.

r = 0.248). Larger quadratic coefficients indicate a wider N1 amplitude deflection and thus more temporal variability across trials. However, there was no difference in the mean quadratic coefficients between age groups ($t_{37} = 1.44$, $p = 0.159$, r = 0.230; Fig. 6A). This result indicates that the difference in overall N1 amplitude between age groups cannot be due to differences in intertrial response timing.

The present study controlled for overall audibility of the tones between age groups by presenting tones at 55 dB above the individual sensation level. Nevertheless, Fig. 1A indicates that hearing thresholds at the stimulation frequency (1000 Hz) were slightly elevated for older participants compared with younger participants ($t_{37} = 5.30$, $p < 0.001$, r = 0.657), and older participants received tone stimuli that were on average 9.6 dB louder. To investigate whether the difference in overall N1 amplitude between age groups is due to a ~10-dB sound intensity difference, we tested 10 of the 18 older participants a second time (~6 months between sessions; repeat audiometry revealed no clinically relevant hearing loss at the 1000-Hz stimulation frequency) and conducted the same experiment with the exception that tones were presented at 45-dB sensation level (SL; instead of 55-dB SL). N1 amplitudes in response to tones presented at 45-dB SL (−4.18 μV ± 1.49 SD; $t_{29} = 2.69$, $p = 0.012$, r = 0.447) and to those presented at 55-dB SL (−4.37 μV ± 1.51 SD; $t_{29} = 3.07$, $p = 0.005$, r = 0.495) were larger for older compared with younger participants (−2.88 μV ± 1.14 SD). No difference was found between responses elicited by tones presented at 45-dB SL versus 55-dB SL ($t_9 = 0.98$, $p = 0.354$, r = 0.310; Fig. 6B). Hence, older participants appear to have exhibited larger N1 amplitudes regardless of the precise sound level (see also Herrmann et al., 2013b).

Finally, we examined whether overall N1 amplitude differences between age groups are due to differences in audiometric HLs. To this end, we selected 8 participants in each age group for which the audiometrically assessed HL at 1000 Hz (stimulation frequency) was matched between age groups (younger, 4.06 HL ± 4.99 SD; older, 4.69 ± 5.08 SD; $t_{14} = 0.25$, $p = 0.808$, r = 0.066). Neural responses were averaged across all conditions, and the overall N1 amplitude was again significantly larger in older compared with younger participants (younger, −2.60 μV ± 1.55 SD; older, −4.83 μV ± 1.49 SD; $t_{14} = 2.94$, $p = 0.011$, r = 0.618; Fig. 6C). Hence, increased overall N1 magnitude differences between age groups are unlikely to be due to differences in audiometric HL.

3.5. Adaptive exponential integrate-and-fire model reproduces N1 temporal context and aging effects

To qualitatively describe the N1 temporal context and aging effects, we made use of the adaptive exponential integrate-and-fire model (Brette and Gerstner, 2005). Fig. 7A shows the membrane potential (V) and the adaptation variable (w) as a function of time for each temporal context (only the first 35 seconds are depicted). The inset in Fig. 7A depicts an example of the spikes elicited by the stimulation input current.

We calculated the mean firing rate for each onset-to-onset interval separately for the regular and the irregular temporal contexts and separately for the accelerating and the decelerating segments of the regular context (Fig. 7B). Firing rates for younger participants were obtained using an adaptation time constant of 10 seconds (τ_w), whereas firing rates for older participants were obtained using $\tau_w = 6$ seconds. Adjustment of the adaptation time constant for the age groups qualitatively reproduced the empirical findings of the N1 data. Note, however, that we did not quantitatively fit the spiking activity to EEG responses and the parameters are thus broad estimations. Adjustments of other model parameters resulted in inconsistencies between the modeled responses and the observed N1 temporal context and aging effects.

The results obtained using the model were as follows: First, firing rates were overall larger in irregular compared with regular temporal contexts. Furthermore, firing rates increased as a function of onset-to-onset interval duration (Fig. 7B). Similar to the N1 analyses, we calculated the dynamic response range for each temporal context (regular, irregular). The dynamic response range was larger for regular compared with irregular temporal contexts and slightly larger for older compared with younger participants (Fig. 7C, top). In addition, we calculated the mean firing rate for accelerating and decelerating segments of the regular temporal context (i.e., average across onset-to-onset intervals). Firing rates were larger for accelerating than decelerating segments and the difference between accelerating and decelerating segments was larger for younger than older participants, reflecting a larger firing rate modulation by temporal context for younger participants (Fig. 7C, bottom). Finally, firing rates were overall larger for older compared with younger participants.

To summarize, the adaptive exponential integrate-and-fire model reproduces the main features observed in the human N1 responses in different temporal contexts and different age groups.

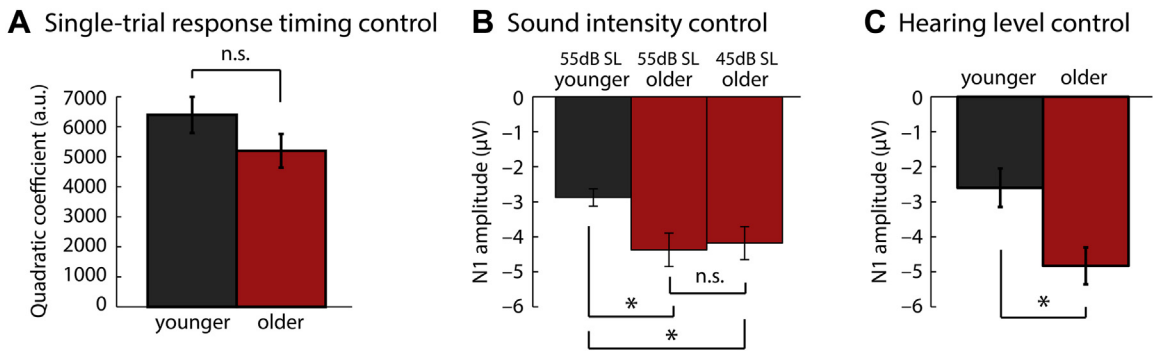

Fig. 6. Potential contributions to overall N1 differences between age groups. (A) Quadratic coefficients from quadratic function fits to the N1 deflection. The deflection is expected to be wider (smaller quadratic coefficient) if single-trial response timing is more variable. No difference was found. (B) Overall N1 amplitudes for younger and older adults. Sound intensity was controlled for audibility across age groups (55-dB SL). As a consequence, older adults received sounds that were on average ~10 dB louder than for younger adults. Ten older adults took part in an additional second recording session during which sounds were presented with a 10 dB decreased sound intensity at 45-dB SL. Both bar graphs for older adults reflect the mean across the 10 participants that took part in the two sessions. (C) Overall N1 amplitudes for a subset of younger and older adults (each N = 8) for which audiometrically assessed hearing levels were matched. Error bars reflect SEM. *$p < 0.05$. Abbreviations: n.s., not significant; SEM, standard error of the mean.

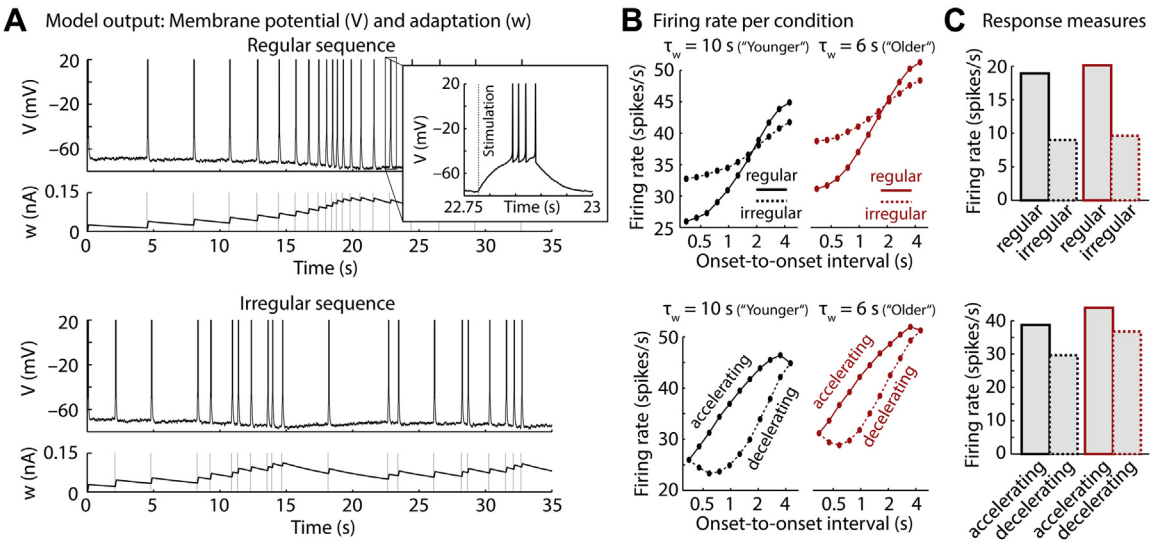

Fig. 7. Adaptive exponential integrate-and-fire (aEIF) model qualitatively reproduces the current N1 data. (A) Model outputs as a function of time separately for regular and irregular sequences ($\tau_w = 10$ seconds; "younger" participants). Outputs: membrane potential (V) and adaptation variable (w). Gray vertical lines reflect event onsets (only the first 35 seconds are depicted). The inset shows spiking in response to input stimulation. (B) Mean firing rate estimated for regular versus irregular temporal contexts and for accelerating versus decelerating sequence parts. (C) Top: dynamic response range calculated as the difference between the maximum and minimum firing rate across onset-to-onset intervals. Bottom: mean response for accelerating and decelerating segments (i.e., averaged across onset-to-onset intervals). Simulated data for younger versus older participants resulted from using $\tau_w = 10$ seconds or $\tau_w = 6$ seconds as adaptation time constant, respectively.

Critically, only adjustment of the adaptation time constant parameter (τ_w) was able to account for the temporal context and the aging effects; the value of the time constant parameter needed to be larger for younger compared with older participants. In other words, the extended temporal stimulation history had less influence on the response magnitude elicited by a sound for older compared to younger adults.

4. Discussion

In the present EEG study, we investigated how aging affects neural adaptation in auditory cortex. We observed long-lasting response adaptation (beyond the interval directly preceding a tone) causing neural-response sensitivity to differ between different temporal contexts. Critically, aging was accompanied by overall larger and less variable responses, a larger dynamic response range, and lower sensitivity to temporal context. Computational modeling suggested shortened recovery time from neural adaptation in older participants.

4.1. Neural response modulation by temporal context

In line with studies using isochronous stimulation (Budd et al., 1998; Czigler et al., 1992; Davis et al., 1966; Hari et al., 1982; Rosburg et al., 2010), we observed that N1 and P2 amplitudes increased with longer intervals between tones. Critically, our data show long-lasting N1 response adaptation beyond the interval directly preceding a tone. Long-lasting adaptation led to a reduced response range in irregular compared with regular temporal contexts, and to larger responses in accelerating versus decelerating segments of the regular context. Previous studies that contrasted temporally regular versus irregular stimulation have observed diverse results, with some studies showing larger responses in irregular stimulation contexts (Papanicolaou et al., 1985a; Rothman et al., 1970; Schwartze et al., 2013) while others showed no difference (Nelson and Lassman, 1977; Papanicolaou et al., 1985b). Our data are in line with previous findings on fast presentation rates (≤1 second intervals; Costa-Faidella et al., 2011a; Okamoto and Kakigi, 2014; Zacharias et al., 2012), suggesting nonlinear brain responses that depend on the temporal structure in which tones are presented.

In particular the studies by Costa-Faidella et al. (2011a) and Zacharias et al. (2012) have revealed decreased response modulations for irregular compared with regular temporal stimulation contexts comparable with the current findings. Those alterations in neural responses due to changes in the temporal structure of sound presentations have been discussed in the context of predictive processes (Costa-Faidella et al., 2011a; Lange, 2013; Schwartze et al., 2013). However, the fact that the adaptation model used here captures the N1 temporal-context effects (regular vs. irregular) suggests caution in interpreting N1 response modulations as being related to sensory predictions as compared with neural adaptation. Whether neural adaptation mechanistically supports the generation of sensory predictions is a question that requires further studies in which manipulation of predictability are not confounded with physical stimulus manipulations (see also Todorovic et al., 2011).

Given our data, it seems surprising that previous studies revealed only an N1 decrease from the first to the second sound in a stimulus train with constant onset-to-onset intervals, but no further decrease for subsequent sounds (Budd et al., 1998; Lagemann et al., 2012; Rosburg, 2004). In some studies, a gradual response decrease is visually observable (Rosburg et al., 2006; Zhang et al., 2011) which is in line with single-neuron recordings (Duque and Malmierca, 2015; Gutfreund, 2012) and the current observation of long-lasting adaptation. Using temporally variable (compared to isochronous) stimulation, as was done here, appears to allow for a much more refined exploration of long-lasting neural adaptation.

In previous adaptation studies, modulation of P2 amplitudes largely paralleled that of N1 amplitudes (Hari et al., 1982; Herrmann et al., 2013a; Picton et al., 1978). However, the current data show that the N1 and the P2 amplitude modulations within accelerating and decelerating segments differ qualitatively. Whereas N1

amplitudes were overall larger in the accelerating than in the decelerating segments, such a difference was not observed for P2 amplitudes. Instead, P2 amplitudes were more strongly modulated by onset-to-onset intervals in the decelerating segments, which we did not observe for N1 amplitudes. The current data suggest that different neuronal populations generate N1 versus P2 responses (Hoshiyama et al., 2007; Pantev et al., 1996) with different neural populations exhibiting different adaptation properties (Roth et al., 1976). In particular, P2 response patterns could not be modeled using the single-neuron model that successfully captured the N1 response patterns, which might be due to more complex interactions among neurons (potentially exhibiting a great variety of adaptation properties) within the P2-generating neural circuitries. The present study demonstrates that differences between the neural N1 versus P2 responses might be best examined using temporally variable tones sequences as compared to isochronous stimulation.

4.2. Models of N1 response adaptation

The present study used a single-neuron model (Brette and Gerstner, 2005; Cohen, 2014; Hildebrandt et al., 2015; Walcott et al., 2011) and showed that the neuron's response output qualitatively captures the temporal context and aging effects on human N1 responses observed here. Since the relation between spiking activity of a modeled single neuron and the EEG field potential generated by the synchronized activity of many neurons is not straightforward (Buzsáki et al., 2012; Einevoll et al., 2013), our modeling approach is explicitly qualitative and merely aims to emphasize that electrophysiologically established adaptation mechanisms can capture human EEG response modulations. Nevertheless, spiking activity and field potentials are functionally related. Spiking activity is commonly associated with the output of a neuron or neuronal population, whereas the field potential largely reflects synaptic activity (among other aspects), and thus contains information about the input to a neuron or neuronal population, which is integrated in the soma to determine spiking (Bullock, 1997; Buzsáki et al., 2012; Logothetis and Wandell, 2004; Logothetis et al., 2001). Hence, the general functional properties modeled here using spiking activity are likely also present in the field potentials picked up by the EEG electrodes on the scalp.

Previous EEG and/or magnetoencephalography studies modeled adaptation using an exponential function fit to N1 amplitudes as a function of onset-to-onset interval (Lü et al., 1992; Mäkelä et al., 1993; Sams et al., 1993). The exponential function fit assumes that neural populations are fully adapted at sound presentation, whereas the present study shows that the extended temporal context beyond the directly preceding interval affects N1 responses. N1 adaptation was recently modeled using two exponential functions and a variable simulating a neuron pool (Zacharias et al., 2012), but our aging data in particular were not well captured by this model. The model used here incorporates a long adaptation time constant such that an input influences the response magnitude beyond multiple subsequent inputs. Neurons exhibiting long-lasting adaptation spanning from seconds (Abolafia et al., 2011) to tens of seconds (Costa-Faidella et al., 2011b; Netser et al., 2011) have been observed along the auditory pathway. The current data suggest that neurons generating the N1 response in auditory cortex also have long-lasting adaptation properties. Consequently, the response magnitude to any given sound is a nonlinear function of the extended temporal history of preceding sounds. The neural mechanism(s) underlying neural adaptation of auditory N1 responses, and changes in these with age, might be related to neural inhibition, synaptic depression, or changes in potassium currents (Abbott et al., 1997; Abolafia et al., 2011; Hildebrandt et al., 2011; Loebel et al., 2007; McEvoy et al., 1997).

4.3. Aging affects neural adaptation in auditory cortex

We observed several age-related differences in neural responses: (1) older adults showed generally larger but less variable, responses; (2) the dynamic response range was larger in older adults; and (3) older adults showed reduced sensitivity to temporal context (accelerating versus decelerating). We show that faster recovery from neural adaptation in auditory cortex can account for our aging effects.

Overall larger responses for older adults are consistent with decreased neural inhibition along the auditory pathway accompanying aging (Caspary et al., 2008). That is, degradation of the auditory periphery leads to augmented responses in auditory cortex (Bidelman et al., 2014; Herrmann et al., 2013b; Stolzberg et al., 2012; Tremblay et al., 2003; Zhang et al., 2009), likely driven by a release of cortical inhibition (Caspary et al., 2008; Llano et al., 2012; Takesian et al., 2012). In line with the current data, there have been previous reports of larger N1 responses for older adults or adults with hearing loss (Anderer et al., 1996; Bidelman et al., 2014; Harkrider et al., 2005; Herrmann et al., 2013b; Sörös et al., 2009; Tremblay et al., 2003), although the literature is mixed (Bennett et al., 2004; Czigler et al., 1992; Ford et al., 1979; Harris et al., 2008; Papanicolaou et al., 1984).

Some of the variability in previous findings regarding the age-related changes in N1 amplitude might be related to differences in stimuli that were presented (e.g., sounds with different onset times, Tremblay et al., 2003; or tone frequencies, Harris et al., 2007, 2008), the extended temporal stimulation history (Kisley et al., 2005; Papanicolaou et al., 1984; the current study), response types (elicited by a stimulus onset vs. a stimulus change, Tremblay and Ross, 2007), response measures (N1-P2 difference vs. analysis of individual event-related potential components, Harris et al., 2007; note that the present data show a functional separation here between the N1 and P2 adaptation), and/or in the mean age of the sample (<65, Herrmann et al., 2013b, the current study; >75, Papanicolaou et al., 1984). Here, we have excluded potential sources (temporal variability of single trials; sound level; audiometric hearing thresholds) that could have contributed to response increases for older listeners. Other and potentially less quantifiable contributions to the differences between studies might come from random participant factors that might be more evident in studies with smaller sample sizes ($N \leq 9$, Czigler et al., 1992; Papanicolaou et al., 1984; vs. $N \geq 13$, Bidelman et al., 2014; Herrmann et al., 2013b; the current study). In particular variable degrees of cochlear neuropathy (so-called "hidden hearing loss"; Schaette and McAlpine, 2011; Viana et al., 2015) might add to listener-specific factors resulting in a heterogeneous group of older people (Tremblay and Ross, 2007).

Nevertheless, based on the available literature, there does not seem to be a unique feature that can account for all differences in age-related alterations of the N1 response between studies; this suggests a complex interaction among acoustic features, listening contexts, and listener-specific factors (e.g., hidden hearing loss). In addition, the present study shows that the same neural mechanism can underlie very different effects of age on the observed N1 amplitude (reduced sensitivity to temporal context; overall larger amplitude; larger dynamic response range). It is thus important to continue the approach outlined here, linking human EEG responses and age-related changes therein to electrophysiologically motivated models that simulate neural activity.

Similar to the overall cortical response increase, the increase in dynamic response range for older adults was predicted by faster

recovery from adaptation in the neuron model. Previous studies using sound intensity manipulations revealed increases in the dynamic response range after noise exposure in animals (Popelár et al., 1987; Syka et al., 1994) and also in older human adults (Laffont et al., 1989). Furthermore, the response range related to sound intensity is larger for nonadapted compared with adapted neural populations (Keidel and Spreng, 1965; Müller and Stange, 1971). These previous findings, together with our observations, suggest that neural gain (i.e., the relation between stimulus input and neural output) increases for neural populations that exhibit reduced adaptation, such as observed here for older adults. That older adults showed decreased neural sensitivity to temporal context (i.e., a reduced response difference for accelerating versus decelerating segments) appears to be a consequence of faster recovery from neural adaptation.

Reduced inhibition in auditory cortex has been proposed to compensate for degradation of afferent inputs after sensory decline in aging (Caspary et al., 2008; Gao et al., 2015; Herrmann et al., 2013b). An independent line of work shows that neurons in auditory cortex take over visual and somatosensory functions after deafferentation through hearing loss (Allman et al., 2009; Ptito et al., 2012). Both aspects, reduced inhibition in auditory cortex and plastic functional assimilation of auditory cortex neurons, might reflect long-term adaptive brain functions accompanying sensory decline. A specific, albeit speculative, hypothesis is that reduced inhibition increases the likelihood that neurons rewire to support functions in addition to auditory functions. Our data are consistent with reduced neural inhibition after sensory decline, but future works is needed exploring neural rewiring in normal aging.

The current data also show a decrease in the variability of the auditory cortex response magnitude for older adults. Neural responses in subcortical structures are commonly more variable and reduced for older than younger adults (Anderson et al., 2012; Bidelman et al., 2014), although these effects are often related to temporal response precision, while our effects are related to the response magnitude. Reduced response variability could be related to a reduced inhibition such that neurons fire more rigorously and synchronously when neural inhibition is diminished. More generally, our data are in line with functional imaging results showing decreased neural response variability for older people (Garrett et al., 2011, 2013; but see Lövdén et al., 2007 for increased behavioral variability) emphasizing the importance of sensory response variability for normal brain function.

The current empirical and modeling data provide strong evidence that healthy human aging is accompanied by reduced neural adaptation. This first demonstration of reduced adaptation in healthy older human listeners provides an important link to animal recordings that show a reduction in neural inhibition time constants, a release of inhibition, and augmented cortical excitability associated with hearing loss and aging (Caspary et al., 2008; Syka et al., 1994; Takesian et al., 2012).

5. Conclusions

The present study demonstrates that auditory cortex EEG responses are largely determined by the temporal context in which the response-eliciting sounds occur. Critically, healthy aging was associated with multiple changes in auditory-cortex response patterns: Increased and less variable response magnitudes, a larger response range, and reduced sensitivity to temporal context. Computational modeling identified a potential mechanism: Reduced recovery time from neural adaptation may underlie these multifaceted changes accompanying aging. The current observations suggest reduced neural adaptation in human auditory cortex as a (mal-) adaptive compensation for sensory decline that accompanies hearing loss and aging.

Disclosure statement

The authors have no conflicts of interest to disclose.

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