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# 40-Hz oscillations underlying perceptual binding in young and older adults

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**Abstract**

Auditory object perception requires binding of elementary features of complex stimuli. Synchronization of high-frequency oscillation in neural networks has been proposed as an effective alternative to binding via hard-wired connections because binding in an oscillatory network can be dynamically adjusted to the ever-changing sensory environment. Previously, we demonstrated in young adults that gamma oscillations are critical for sensory integration and found that they were affected by concurrent noise. Here, we aimed to support the hypothesis that stimulus evoked auditory 40-Hz responses are a component of thalamocortical gamma oscillations and examined whether this oscillatory system may become less effective in aging. In young and older adults, we recorded neuromagnetic 40-Hz oscillations, elicited by monaural amplitude-modulated sound. Comparing responses in quiet and under contralateral masking with multitalker babble noise revealed two functionally distinct components of auditory 40-Hz responses. The first component followed changes in the auditory input with high fidelity and was of similar amplitude in young and older adults. The second, significantly smaller in older adults, showed a 200-ms interval of amplitude and phase rebound and was strongly attenuated by contralateral noise. The amplitude of the second component was correlated with behavioral speech-in-noise performance. Concurrent noise also reduced the P2 wave of auditory evoked responses at 200-ms latency, but not the earlier N1 wave. P2 modulation was reduced in older adults. The results support the model of sensory binding through thalamocortical gamma oscillations. Limitation of neural resources for this process in older adults may contribute to their speech-in-noise understanding deficits.

**Descriptors:** Gamma oscillation, Perceptual binding, Central auditory processing, Thalamocortical network, Aging, Magnetoencephalography

Hearing impairment is a major health concern in older age; it impacts on cognitive function (Idrizbegovic et al., 2011) and well-being (Lindenberger & Baltes, 1994) and is becoming more prevalent as populations enjoy increasing longevity (Pacala & Yueh, 2012). Elderly people often have difficulties in speech comprehension in noise, which seriously impairs daily life function (Schneider, Daneman, & Pichora-Fuller, 2002). Hearing loss in older age, which correlates with speech-in-noise deficits, has been supposed as a primary cause for the speech understanding problem (Humes, 1996). Hearing aids compensate for the loss in sensation; however, often speech-in-noise understanding improves less than expected (Turner & Henry, 2002) because of further age-related physiological and psychological changes such as loudness recruitment, impaired temporal and spectral acuities, and deficits in working memory, attention, and cognition. For example, degraded temporal acuity affects speech comprehension (Fitzgibbons & Gordon-Salant, 1996) and is often measured as gap detection performance, which again decreases with high frequency hearing loss (Glasberg, Moore, & Bacon, 1987). Remarkably, even when accounting for hearing loss, older listeners require a wider gap for detection (Snell, 1997) particularly under complex listening conditions. Older adults can detect short gaps like young listeners when the gap is presented in isolation, but they perform poorly when a gap occurs in the vicinity of other sound changes (Schneider & Hamstra, 1999). Those findings support the hypothesis that changes in higher-order central auditory processing contribute to deficits in speech-in-noise understanding (Frisina, 2001).

An MRI study of word recognition in young and older listeners revealed that the structural integrity of primary auditory cortices is impaired in aging, and it has been concluded that these changes contribute to degraded auditory representations and poorer word recognition in challenging listening conditions (Harris, Dubno, Keren, Ahlstrom, & Eckert, 2009). Other fMRI studies showed increased activity in cognitive brain areas concomitant to reduced activity in primary auditory areas (Wong et al., 2009), which is consistent with impaired sensory input, reduced capacity of sensory

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information processing, and recruitment of compensatory mechanism in healthy aging (Cabeza, Anderson, Locantore, & McIntosh, 2002). From recent studies, it has become clear that aging-related changes in the periphery coexist with changes of central auditory processing at the levels of perception and cognition, and it has been suggested that those factors develop independently (Ouda, Profant, & Syka, 2015).

The central auditory system performs a hierarchy of processing steps for refining spectrotemporal sound information and transforming those into a higher level representation (Rauschecker, 1998; Wessinger et al., 2001; Zatorre, Bouffard, & Belin, 2004). The role of the auditory cortex is integrating acoustical features across time and frequency into a more abstract object representation (Nelken, 2004). Integrating and combining sound items requires that multiple neural representations coexist at cortical level, such as auditory information at multiple time scales. Aging may affect those multiple representations differentially. Previous findings showed that sensory information is represented at the cortical level in older adults with similar high fidelity as in young adults (Alain, McDonald, & Van Roon, 2012; Ross, Schneider, Snyder, & Alain, 2010), and it seems that, as one ages, it becomes more difficult accessing the different components of sensory information and combining them into a meaningful perceptual object. Such listening problems, despite intact hearing, are reflected in a common complaint of older adults: "I can hear you, but I cannot understand what has been said" (Martin & Jerger, 2005). Thus, we can hypothesize that, in addition to peripheral changes, aging may impair central auditory processing at the levels of grouping and integrating acoustical information.

The process of feature integration has been introduced as "binding" first for the visual system (Treisman, 1996). For the auditory system, it has been suggested that synchronized activities in populations of neurons could represent distinct patterns of concurrent sounds (von der Malsburg & Schneider, 1986) and thus solve the cocktail party problem (Cherry, 1953). Expanding the principle of coincident neural firing, it has been considered that coupling between neural networks through synchronous gamma oscillations serves as the neural mechanism underlying sensory binding (Bertrand & Tallon-Baudry, 2000; Buzśaki & Wang, 2012; Engel & Singer, 2001; Herrmann, Fründ, & Lenz, 2010).

Among neuroanatomical structures involved in gamma oscillations, recurrent connections between cortex and thalamus have been proposed as the main mechanism for binding (Llinás, Leznik, & Urbano, 2002). The thalamocortical circuit comprises two types of thalamic neurons, which have been identified based on different immunoreactivity: Thalamic core neurons project to specific cortical areas (e.g., representing the auditory input in tonotopically organized primary auditory areas) while thalamic matrix cells project to wider-spread cortical areas. Interactions between core and matrix units in the thalamus through synchronous oscillation provide a schema of communication between primary sensory areas and higher-order cortical representation (Jones, 2009). Since the mechanism of binding based on gamma oscillation in such thalamocortical circuits has been introduced (Llinas & Ribary, 1993), subsequent studies have discovered the details of the binding circuit. Specifically, inhibitory interneurons, located at the place of termination of inputs from the thalamus at middle or superficial cortical layers, play a key role for generating gamma oscillations within this circuit. Computational modeling demonstrated resonance-like tuning of these neurons in the 40-Hz range (Vierling-Claassen, Cardin, Moore, & Jones, 2010). Local oscillations in these interneurons help maintain gamma-band synchrony in the long-range thalamocortical loop, even though the large pyramidal cells typically fire at a much slower rate below 10 Hz (Sukov & Barth, 2001). Gamma oscillations modulate the membrane potential of the pyramidal cells, such that they become more sensitive and start firing preferentially at a certain phase of the gamma oscillation. This principle of phase-sensitive timing has been demonstrated in vivo with an optogenetic study, in which fast-spiking interneurons in mice were stimulated with light at a steady 40-Hz rhythm (Cardin et al., 2009). This caused 40-Hz modulation of the local field potential, which in turn made neurons in the somatosensory cortex sensitive to whisker stimulation at a specific phase of the 40-Hz stimulus (Cardin et al., 2009). Firing at gamma rates can be maintained in the population, when cortical cells fire each at a slow rate, though precisely at a common phase of the gamma oscillation. Such neural firing at a specific phase of gamma oscillation has been proposed as a general concept of neural communication and especially sensory binding (Fries, 2009; Nadasdy, 2010).

Indeed, the relation between gamma oscillations and perception has been demonstrated in experimental studies. When changing the delay between two clicks in a stimulus pair, the transient gamma responses elicited by each click fused into common oscillations at the perceptual threshold, where both clicks were no more separated, and the pair was perceived as one auditory object (Joliot, Ribary, & Llinás, 1994). Similarly, we have shown recently for amplitude-modulated sound stimuli that transient evoked responses at slow modulation rates fused into common oscillations when the modulation rate was increased, and perception changed through three distinctive stages from loudness fluctuation in single beats, to flutter sensation, and to roughness (Miyazaki, Thompson, Fujioka, & Ross, 2013). Notably, the latter transition occurred at gamma frequencies around 40 Hz. Thus, the current study is aimed at further studying central auditory processing in cortical responses recorded with 40-Hz rhythmic auditory stimulus, often referred to as auditory steady-state responses (ASSR).

The 40-Hz ASSR is recorded with a high signal-to-noise ratio in response to amplitude-modulated sound stimuli using EEG (Picton, John, Dimitrijevic, & Purcell, 2003) and magnetoencephalogram (MEG; Ross, Borgmann, Draganova, Roberts, & Pantev, 2000). While 40-Hz ASSR have been closely associated with gamma oscillation in thalamocortical circuits (John, 2002; Plourde, Villemure, Fiset, Bonhomme, & Backman, 1998), the direct link between gamma and ASSR has been made mainly in neuropsychiatry studies examining the integrity of the gamma system (Başar, 2013; O'Donnell et al., 2013; Ribary, 2005; Ribary et al., 1991; Ribary, Llinás, Kluger, Suk, & Ferris, 1989). Regarding the question as to whether 40-Hz ASSR reflects oscillatory gamma mechanisms, it might be helpful to consider the traditional view of distinguishing oscillations into stimulus phase-locked evoked responses and less phase-locked induced responses. Earlier research proposed that the former is related to sensory processing and the latter to higher-order processing (Bertrand & Tallon-Baudry, 2000). This classification was closely related to subdividing event-related responses into exogenous and endogenous components. However, it has always been pointed out that an overlap between these response types exists specifically for the process of transforming sensation into perception (Hillyard, Picton, & Regan, 1978). Recent research adopted evoked gamma oscillations for perception-related research (Bidet-Caulet et al., 2007; Cardin et al. 2007) under the updated view that evoked and induced oscillations share a common generation mechanism. Therefore, our hypothesis is that the rhythmic stimulus, eliciting the ASSR, synchronizes

multiple types of gamma oscillation that play multiple roles at sensory level and beyond for higher-order perception.

Previous studies in humans suggested that multiple components contribute to the 40-Hz ASSR (Gutschalk et al., 1999; Herdman et al., 2002). Moreover, several aspects of findings demonstrate commonalities between 40-Hz ASSR and gamma oscillations, thus supporting the hypothesis that their generation mechanisms involve the thalamocortical circuitry. First, the transfer characteristics of the ASSR with a peak at 40 Hz (Picton et al., 2003; Ross et al., 2000) resemble closely the frequency characteristics of the fast-spiking interneurons, supposed to be the main source of gamma oscillations (Vierling-Claassen et al., 2010). Second, the temporal dynamics of the onset transition of the 40-Hz ASSR are not compatible with linear combination of sensory inputs and suggest additional gamma components (Ross, Picton, & Pantev, 2002). Third, change in a stimulus feature (Ross, 2008; Ross & Pantev, 2004) or a concurrent stimulus (Ross, Herdman, & Pantev, 2005) resets the 40-Hz oscillation, as it had been described as the mechanism of the binding circuit reacting to changes in the sensory environment (Llinas & Ribary, 1993). Based on the findings that a concurrent stimulus can reset the 40-Hz oscillations, we hypothesize that concurrent noise interferes with 40-Hz oscillations at a central level and, if so, such central interference may differ between young and older adults.

In hearing research, it has been well known that concurrent noise affects representation of a target sound at levels of the basilar membrane and the auditory nerve. The related elevation of the hearing threshold is termed *peripheral masking* (Tanner, 1958). It is largest when the spectral energies of the target and noise overlap (Fletcher, 1940), and it is therefore synonymously termed *energetic masking*. Masking by noise in the contralateral ear is termed *central masking* (Wegel & Lane, 1924), because of the lack of interference at the periphery. Central masking is subtler than peripheral masking when noise is stationary, such as continuously presented broadband noise, which elevates the threshold by a few dB only (Mills, Dubno, & He, 1996). However, when noise contains temporally structured sounds with higher-level similarities to the target sound, it severely affects perception, and is termed *informational masking*. In this case, both the target and the masker are audible, but the listener is confused and cannot disentangle features of one or the other sound (Kidd, Mason, & Arbogast, 2002). Similarity-based interference occurs at the acoustic, phonological, and semantic levels (Durlach et al., 2003). Because our interest in the current study is central masking below the level of semantics, we decided to use multitalker babble noise of the voices of multiple talkers engaged simultaneously in conversations (Wilson, 2003). This type of noise is particularly important here because it has been shown to significantly reduce speech intelligibility in aging listeners without hearing loss or cognitive impairment while they were not affected by energetic masking using broadband noise (Rajan & Cainer, 2008).

The current study used MEG and examined auditory 40-Hz oscillations as an objective indicator for central auditory processing in young and older listeners, with and without concurrent multitalker noise. Specifically, we examined the temporal dynamics of ASSR amplitude and phase when listening to gaps in sound stimuli because temporal processing is highly relevant for speech perception (Rosen, 1992). We hypothesized that noise would affect integrative processes reflected in 40-Hz oscillations where the aging brain may exhibit selective neural deficits. Furthermore, impaired perceptual processes in aging would also be reflected in the obligatory auditory evoked responses. Therefore, we examined also auditory evoked P1-N1-P2 waves at 50-, 100-, and 200-ms latency after the gap from the same MEG recording. Our approach was using a complex auditory stimulus, and investigating multiple types of simultaneously evoked cortical responses. With respect to the 40-Hz oscillations, we employed sophisticated data analysis to disentangle different functional components. We then related these responses to different stages of central auditory processing by correlation between behavioral measures. Our results support the role of gamma oscillations for central auditory processing and for speech understanding in noise in the elderly.

## Method

### Participants

Twenty-four healthy native English-speaking volunteers participated in this study. Twelve were in the age range between 19 and 29 years (mean 23.1 years, six female, six male), and 12 were between 60 and 78 years of age (mean 67.8 years, six female, six male). All participants provided written consent after they were informed about the nature of the study, which was approved by the Research Ethics Board at Baycrest Centre.

### Psychoacoustic Tests

We employed behavioral tests of spectral and temporal acuity and speech-in-noise performance. Spectral acuity was tested with detection of a mistuned component in a complex sound composed from the 11 harmonics of a 220-Hz tone (Alain et al., 2012; Moore, Glasberg, & Peters, 1986), which was presented at 80 dB sound-pressure level (SPL). The third harmonic (nominal 660 Hz) was modified in an adaptive procedure to have 1% to 16% higher or lower frequency ($\Delta f = 6.6$ Hz to 96 Hz). Participants indicated whether they perceived two sounds, which were the buzzing harmonic complex and an additional pure tone of the mistuned harmonic, or whether they heard a single buzzing sound only.

Temporal acuity was tested with a two-alternative forced-choice gap detection task, using brief 1000-Hz tones composed of 20-ms leading and trailing markers and the gap duration ranging between 1 ms and 10 ms. Details about the stimuli have been reported previously (Ross et al., 2010; Schneider & Hamstra, 1999).

We used the Quick-SIN test (Killion, Niquette, Gudmundsen, Revit, & Banerjee, 2004) for word understanding in noise. The Quick-SIN test comprises short sentences containing five keywords each, which were binaurally presented, embedded in four-talker babble noise at signal-to-noise ratios of 0 dB to 25 dB in 5-dB steps.

### Auditory Stimuli for MEG

Participants listened to 400-Hz tones with 40-Hz sinusoidal amplitude modulation (AM, modulation depth $m = 1.0$), which reliably elicit 40-Hz ASSR (Hari, Hämäläinen, & Joutsiniemi, 1989; Picton, Skinner, & Champagne, 1987; Rees, Green, & Kay, 1986; Ross et al., 2000). We employed an AM envelope gap paradigm for studying the temporal dynamics of the 40-Hz response. In particular, such stimulus gaps have been shown to reset the ongoing 40-Hz oscillations (Ross & Pantev, 2004). Moreover, the stimuli were designed to elicit sequences of P1-N1-P2 responses to the sound onset and the subsequent stimulus gaps. It should be noted that, while we expected the task performance to decrease with masking, the task was designed to maintain participants' vigilance

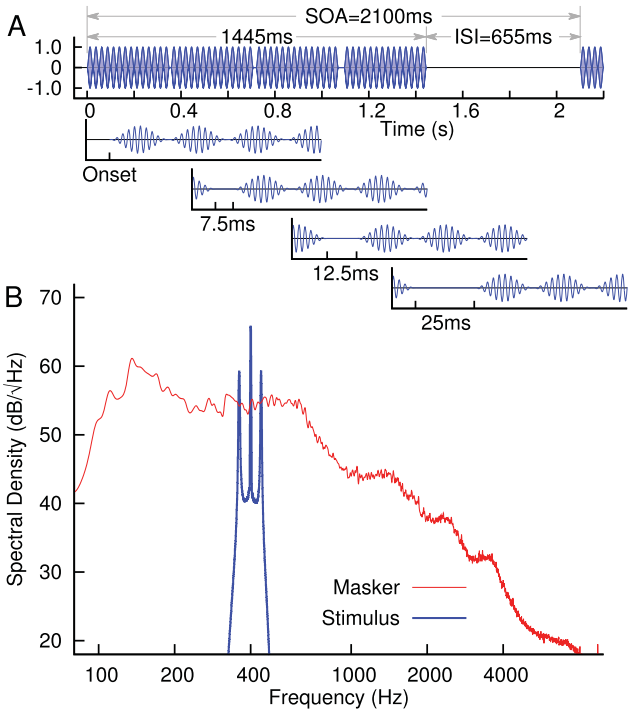


**Figure 1.** Time series and spectra of auditory stimuli. A: Stimulus sequence consisting of four bursts of 40-Hz amplitude modulated (AM) 400-Hz tones of 350-ms duration (equivalent to 14 periods of 40-Hz AM). The AM bursts were separated by gaps of 7.5-, 12.5-, and 25-ms duration, respectively. Each sequence contained the three gaps in random order. Sequences of 1,445-ms duration were separated by an interstimulus interval (ISI) of 655 ms. Inset diagrams illustrate on a finer time scale the time courses of the stimulus onset and the AM gaps. B: The amplitude spectrum of the AM stimulus (blue lines) showed three distinct lines at the carrier frequency of 400 Hz and side lines at 360 and 440 Hz. The mean amplitude spectrum of the contralateral masking sound (red line) was almost flat around the stimulus and decreased by 8 dB/octave above 700 Hz.

during the MEG recording, but not to rigorously evaluate the integrity of central auditory processing.

The stimuli were presented for 1,445-ms duration, while three brief gaps with durations of 7.5 ms, 12.5 ms, or 25 ms were inserted into the sound envelope every 350 ms in randomized order at each trial (Figure 1A). The combination of the gaps and modulated tones mimicked two features of speech perception, which integrate separate acoustic items (AM bursts) and detect boundaries (gaps) between them.

In order to require attention for the entirety of the task, for 20% of the trials, the longest gap of 25-ms duration was replaced with a period of the AM sound such that only the two shorter gaps occurred in the stimulus sequence. This made the number of gaps in the stimuli unpredictable. Participants were instructed to indicate whether they heard two or three gaps by pressing one of two keys on a response pad with the right hand immediately after the end of the stimulus. Stimuli were presented with an interstimulus interval of 655 ms, resulting in a trial duration of 2,100 ms. The six different sequences with three gaps were repeated 24 times, and the six sequences containing two gaps were presented five times within an experimental block. Each block contained a total of 174 stimulus sequences and had a duration of 365.4 s, approximately 6 min.

The gap paradigm served three purposes: First, the task forced participants to pay attention to the stimuli; second, it allowed examining how masking affected the temporal dynamics of the ASSR; and third, it allowed testing how behavioral performance of gap detection was affected by the noise. Detection thresholds in quiet were found previously as short as about 3 ms (Ross & Pantev, 2004). Commonly, shorter gaps closer to the beginning of the stimulus are more difficult to detect (Schneider & Hamstra, 1999). We expected that gap detection may be more demanding for short gaps at the beginning and the end of a sequence, as has been shown for gaps in the presence of more salient concurrent auditory objects (Leung, Jolicoeur, Vachon, & Alain, 2011).

The stimuli were presented monaurally, and masking noise was presented to the contralateral ear for testing interaction at the level of the central auditory system. The masker was a continuous multitalker noise, which was recorded in a Dutch cafeteria frequented by about 100 guests. Multiple copies of the 235-s recording were concatenated and stored on a CD. The spectral density of the masker was flat around the stimulus frequency and decreased by 8 dB per octave above 700 Hz (Figure 1B).

The intensity of the AM gap stimuli was 72 dB SPL, equivalent to 60 dB above normal hearing level. Stimulus and masker intensity were set for about equal loudness in order to closely mimic the conditions of a conversation in multitalker background, for which the speaker typically adjusts his voice volume to only a few decibels above the background noise (Plomp, 1977). The sensation level for the masking sound was found to be 10 dB higher than for the stimulus in a group of 12 normal-hearing listeners. Therefore, the long-term average of the masker intensity was set to 82 dB SPL. This was also the mean sound intensity at recording the cafeteria noise. The spectral peak of the 400-Hz AM carrier was 10 dB larger than the mean density of the masker spectrum, and the AM side lobes were 4 dB above the masker (Figure 1B).

The AM stimuli and masker were presented using ER3A transducers connected via 2.5 m of plastic tubing and foam earplugs. Stimulus intensity was controlled using a clinical audiometer (GSI-61, Grason Stadler, Eden Prairie, MN) Participants were tested in two MEG sessions on separate days. In the first MEG recording session of about 1 h, eight stimulus blocks were presented to the left ear, and in every second block the masker was additionally presented to the right ear. In the second session, the stimulus was presented to the right ear and the masker to the left ear. Initially, the experimental design consisted of the first session only, which was sufficient for studying the effects of central masking. The second session was included later with the same participants for investigating the effects of masking on ipsi- and contralateral responses. On average, 77 days were spent between the first and second session with a range of 61 to 91 days.

### Data Acquisition

MEG recordings were performed in a silent, magnetically shielded room using a 151-channel whole-head MEG system (CTF-MEG, Port Coquitlam, BC, Canada) at the Rotman Research Institute in Toronto. The detection coils of this MEG device are equally spaced on the helmet-shaped surface and are configured as first-order axial gradiometers (Vrba & Robinson, 2001). After low-pass filtering at 200 Hz, the magnetic field data were sampled at the rate of 625 Hz and stored continuously. Participants were seated comfortably in an upright position with the head resting inside the helmet-shaped MEG device. The head position was registered at the beginning and end of each recording block using three detection coils attached to the participant's nasion and the preauricular points. During each block, participants were instructed to maintain their

head position as best as possible. No data were rejected because of head movements larger than ± 4 mm, defined as the exclusion criterion. This procedure ensured that head movements did not significantly affect the source localization accuracy.

### Data Analysis

Each block of continuously recorded MEG data was subdivided into epochs of 2-s duration (1,250 samples at 625 Hz) containing a 1,445-ms stimulus sequence (Figure 1) and each 280-ms pre- and poststimulus interval (175 samples). Artifact correction was applied to the single trials of magnetic field data using a principal component approach (Kobayashi & Kuriki, 1999). In brief, for each epoch, the MEG data matrix containing $n = 1{,}250$ samples from $k = 151$ sensors was submitted to a singular-value decomposition, $[u,s,v] = svd(\text{MEG})$, resulting in a time series $v_i$ of principal components with the spatial topography $u_i$. If the magnetic field of the $i$th principal component $PC_i = u_i\ s_i\ v_i{}^*$ exceeded the threshold of 2 pico Tesla in at least one channel, it was subtracted from the data. This procedure removed successfully artifacts caused by dental metal and eyeblinks, whose magnetic fields are multiple times larger than the brain activity.

After artifact removal, each trial of MEG data was subdivided into epochs of 800-ms duration (500 samples at 625 Hz) including a 200-ms prestimulus interval. Time zero for the analysis epochs of the auditory evoked response was defined by the initial onset of the stimulus, whereas the epochs for analysis of the gap responses were aligned to the onset following each AM gap. For source analysis, the responses to stimulus onset and the different gap types were averaged and band-pass filtered between 28 Hz and 52 Hz for each repeated block separately, using a fourth-order Butterworth IIR filter with correction of the time delay as implemented in the MATLAB filtfilt function. The resulting averaged MEG showed 40-Hz oscillations of the ASSR with almost constant amplitude during the 200-ms to 350-ms latency interval. Source analysis, applied to the ASSR in this latency interval, was based on the model of spatiotemporal equivalent current dipoles in a spherical volume conductor. Single dipoles in both hemispheres were fitted simultaneously to the 151-channel magnetic field distribution. First, the data were modeled with a mirror-symmetric pair of dipoles. The resulting source coordinates were used as the initial points for fitting the dipole in one hemisphere while the coordinates in the other hemisphere were kept fixed. The last step was repeated with switching between hemispheres until the source coordinates showed no further variation. Dipole fits were accepted if the calculated field explained at least 90% of the variance of the measured magnetic field and if the standard deviation obtained from repeated measurements was less than 8 mm in any Cartesian coordinate. Sixteen estimates for the dipole locations were obtained for each participant from the repeated measurements (i.e., eight blocks × two sessions). Individual source models were constructed from the median ASSR coordinates and the orientation fitted to the individual data. ASSR source waveforms were calculated based on this model. This procedure of source space projection (Ross et al., 2000; Teale, Pasko, Collins, Rojas, & Reite, 2013; Tesche et al., 1995) combined the 151-channel magnetic field data into two waveforms of cortical source strength. The advantage of analysis in the source domain is that the dipole moment is independent of the sensor position. The position of the MEG sensor relative to the participant's head may change between sessions and between participants. This may cause spatial dispersion in group-averaged magnetic field waveforms. In contrast, the waveforms of cortical source activity can be combined across repeated sessions and groups of participants. Time courses of amplitude and phase of the 40-Hz oscillations were obtained as the absolute value and angle of a Hilbert transform applied to the source waveforms. The low-frequency transient responses to sound onsets and the AM gaps were extracted from the source waveforms after 24-Hz low-pass filtering. The amplitude of the P2 response with latency in the 180–200 ms interval and the amplitude of the ASSR were analyzed using repeated measures analysis of variance (ANOVA) with the factors side of stimulation, masking, hemisphere of recording, and gap duration. Statistical results were accepted at $\alpha = 0.05$. All analyses were performed using customized MATLAB programs.

As the term steady state implies, the ASSR are characterized by constant amplitude and phase over time. However, it is important to note that the amplitude and phase of the 40-Hz oscillatory response dynamically change after a stimulus event until they reach the steady state. Therefore, we refer to the response here more generally as evoked 40-Hz oscillations or stimulus-driven 40-Hz oscillations and are using these terms synonymously with the term ASSR.

## Results

### Auditory Performance

Group mean pure-tone hearing thresholds in the young participants were below 10 dB in the 250 Hz to 8000 Hz frequency range. In older participants, thresholds were mildly elevated below 1000 Hz and progressively increased toward higher frequencies (Figure 2A). Differences between ears were less than 15 dB between 250 Hz and 2000 Hz in both groups.

For detection of the mistuned harmonic, the just-noticeable frequency difference increased from 33.7 Hz (5.1% of 660 Hz) in the young to 66.7 Hz (10.1%) in the older participants, as revealed by linear regression analysis, $R^2 = .29$, $F(1,22) = 8.6$, $p = .008$. Despite the significant differences in the group means, some older participants performed similarly to the young and vice versa (Figure 2B).

Gap detection performance was more variable in the older than the young. Only three of 11 older participants needed larger gaps for detection, while eight could detect short gaps like the young (Figure 2C). Quantitative analysis found no significant differences between group means.

The Quick-SIN test revealed that older participants required a 3.5 dB, 95% CI [2.1, 4.9], larger signal-to-noise ratio for speech understanding than young adults (Figure 2D). Regression analysis showed significance for the group difference, $R^2 = .34$, $F(1,22) = 10.9$, $p = .0034$ (Figure 2E). Speech-in-noise performance was correlated with spectral acuity as tested with the mistuned harmonic, $R^2 = .22$, $F(1,22) = 6.15$, $p = .021$.

In addition to the above behavioral testing, participants were required during MEG recording to report the number of envelope gaps within the stimulus sequences. Without masking, young participants reported in 72.2%, 95% CI [64.6, 79.8] of trials the correct number of gaps, while performance in noise dropped to 65.4% (± 5.9%), $F(1,11) = 8.6$, $p = .013$. Older participants reported the correct number of gaps in 73.9% (± 8.4%) of trials without noise and in 65.4% (± 8.8%) with noise, $F(1,11) = 19.6$, $p = .001$. Group mean performances were not different between young and older adults, $F(1,22) = 2.0$, *n.s.*, suggesting that attention and effort made during the MEG recording were compatible across groups.

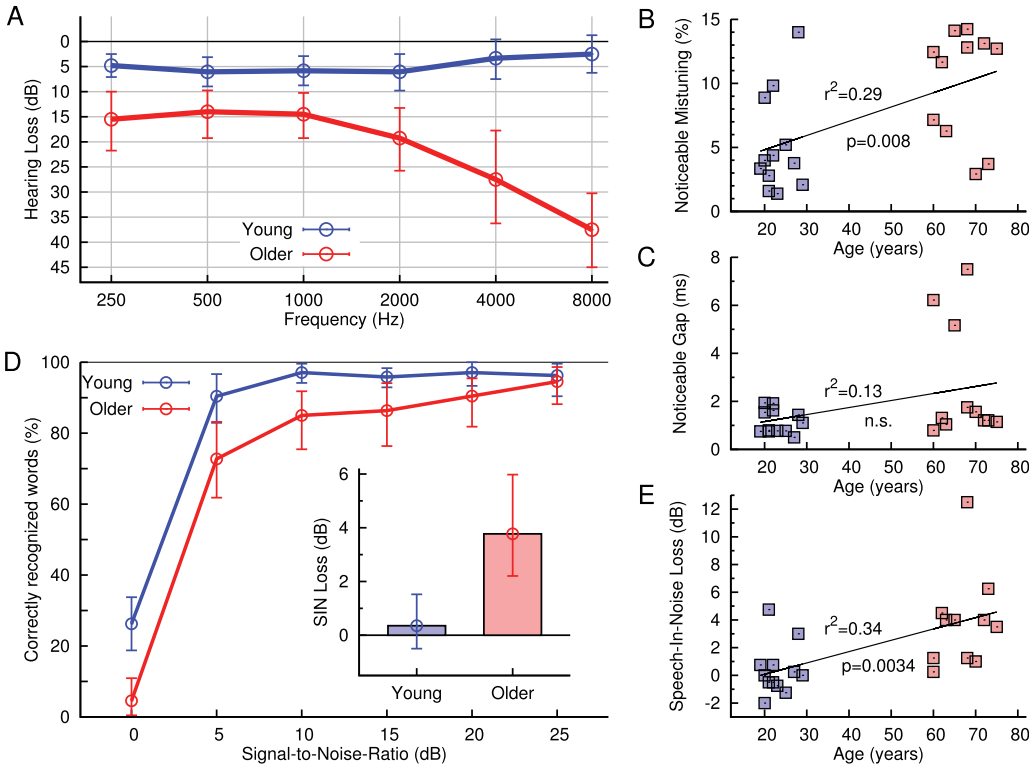


**Figure 2.** Behavioral performance in hearing tests. A: The group mean audiograms, averaged across both ears, for the young and older participants demonstrate elevated thresholds in the older participants and specifically increasing hearing loss toward higher frequencies. The error bars denote the 95% CI for the group means; nonoverlapping error bars indicate that the hearing thresholds were significantly different between groups at all frequencies between 250 Hz and 8000 Hz. B: Spectral acuity was tested by detecting a mistuned harmonic of a harmonic complex sound. The *y* axis shows the amount of mistuning that was required for perceiving a separate tonal sound in addition to the complex sound. In mean, the young could detect 5.1% mistuning (33.7 Hz), while the older participants required 10.1% mistuning (66.7 Hz) for detection; the regression showed a significant difference between the groups. C: Temporal acuity was tested with a gap detection task. Although some older participants required larger gaps for detection, the performance difference between groups was not significant. D: Correctly recognized words in the quick-SIN speech-in-noise test. The inset bar graph shows the group mean loss in speech-in-noise understanding, which was 3.8 dB, 95% CI [2.3, 5.9]) for the older and 0.35 dB, 95% CI [-0.5, 1.5]) for the young listeners. E: The individual speech-in-noise loss progresses with increasing age.

### Cortical Sources of 40-Hz Oscillations

We modeled the sources of 40-Hz responses with bilateral equivalent current dipoles for each individual participant. The group mean source locations in the Talairach coordinate system were 49.5 mm (right), 16.7 mm (posterior), 4.1 mm (superior), and −42.7 mm, 18.1 mm, and 6.9 mm (left). Centers of activity were located in bilateral superior temporal gyri (Brodmann areas 41 and 42) close to primary auditory cortices. Differences in mean coordinates between the age groups were less than 4 mm in any direction. The findings of slightly more anterior-located sources in the right hemisphere in young, $t(11) = 16.9$, $p < .0001$, and older adults, $t(11) = 2.8$, $p = .018$, reflected the characteristic asymmetry of auditory cortices (Penhune, Zatorre, MacDonald, & Evans, 1996) and demonstrated the reliability of the source estimation. Time series of cortical source activities were obtained based on the individual source estimates and measured in nAm, the unit of the dipole moment.

### Auditory Evoked Responses to Sound Onsets

The averaged sound onset responses, low-pass filtered at 24 Hz, revealed the characteristic sequence of auditory evoked P1, N1, and P2 waves with about 50-ms, 100-ms, and 200-ms latency, respectively, and a later long-lasting negativity, called the sustained field. From visual inspection of the grand-averaged left and right auditory cortex waveforms (Figure 3), it was noticeable that masking attenuated the amplitudes for all conditions, but the amount of reduction was not uniform across the different waves of the evoked response. Also, the waveform morphology was remarkably different between age groups. These differences were statistically analyzed by comparing peak amplitudes and latencies across groups and experimental conditions.

Mean P1 amplitudes were almost identical in both groups (young: 8.0 nAm, older: 9.0 nAm, $F(1,22) = 0.4$, *n.s.*), whereas the latencies were even shorter in the older (50 ms) compared to young (57 ms) participants, $F(1,22) = 8.6$, $p = .008$. No effects of masking or the side of stimulation were significant for the P1 responses.

The mean N1 amplitudes were larger in the older participants (9.6 nAm) compared to the young (3.8 nAm), $F(1,22) = 9.4$, $p = .0004$. N1 amplitudes were not significantly affected by contralateral masking, $F(1,22) = 2.9$, $p = .11$, and an interaction between group and masking was not significant, $F(1,22) = 1.0$, *n.s.* Also, N1 latencies were similar for older (108 ms) and young (105 ms) participants, $F(1,22) = 0.5$, *n.s.*

The ANOVA for the P2 peak amplitudes with the between-participants factor age and within-participant factor masking revealed an effect of masking, $F(1,22) = 44.2$, $p < .0001$; P2

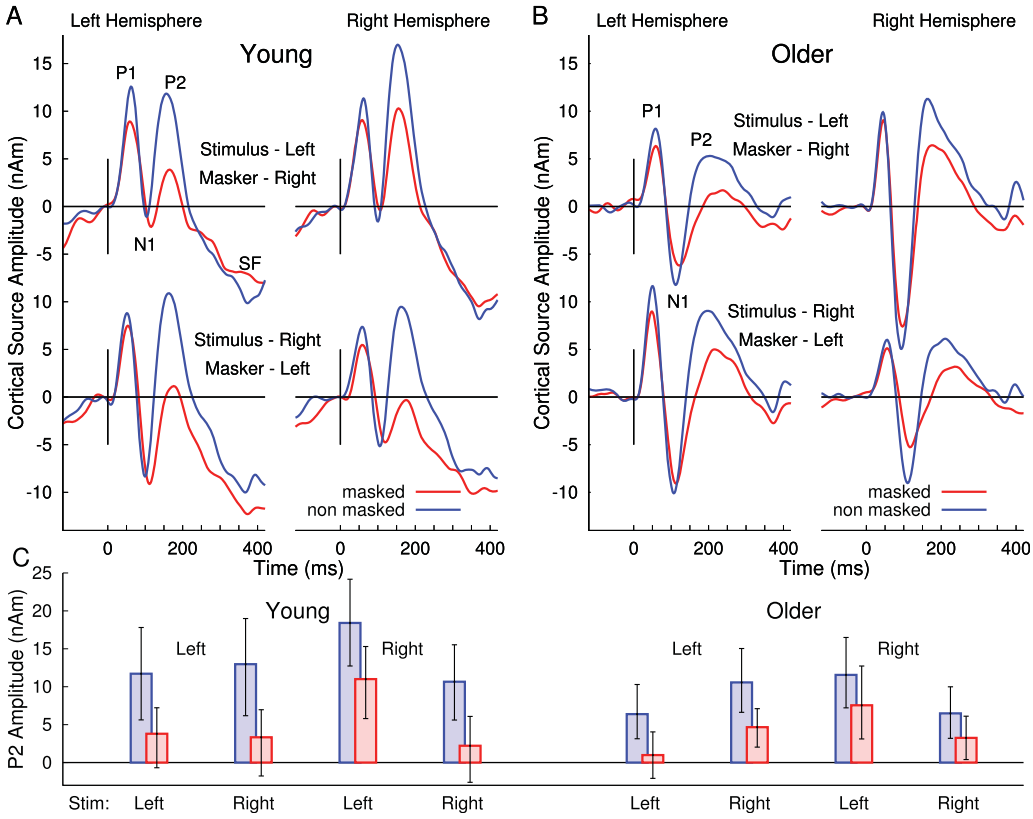


**Figure 3.** Auditory evoked responses to the sound onset. The left and right auditory cortex waveforms were low-pass filtered at 24 Hz and showed characteristic P1-N1-P2 waves to left and right ear stimulation. Generally, the response amplitudes were reduced in presence of the masker, and this effect seem**ed** to be stronger expressed around the latency of the P2 wave than at earlier latencies of the P1 and N1 waves. The modulation of the P2-amplitude was larger in the young compared to the older group.

amplitudes were generally larger without masking (Figure 3C). The ANOVA revealed no effect of age, $F(1,22) = 1.5$, *n.s.*, and a tendency for an interaction between age and masking $F(1,22) = 3.8$, $p = .065$, because of larger P2 modulation in the young. When the contralateral masker was present, the mean P2 amplitudes were not significantly different, $t(46) = 0.43$, *n.s.*, between young (5.0 nAm) and older (4.2 nAm) participants. In contrast, without the masker, P2 was larger in the young (13.5 nAm) than older (8.8 nAm) participants, $t(46) = 2.05$, $p = .046$. An interaction between ear of stimulation and hemisphere of recording, $F(1,11) = 33.4$, $p < .0001$, was caused by larger P2 amplitudes contralateral to stimulation than ipsilateral (Figure 3C). However, ear of stimulation had no main effect on the P2 amplitude and did not interact with the effect of masking, $F < 0.5$, *n.s.* The P2 latency was prolonged in the older participants (195 ms) compared to the young (164 ms), $F(1,22) = 19.8$, $p = .0002$.

### Amplitudes of 40-Hz Oscillations

The amplitude modulation of the stimulus elicited clear responses at the 40-Hz modulation frequency. Prominent characteristics of the waveforms are illustrated in Figure 4. After stimulus onset, the 40-Hz amplitude developed gradually over time and reached its maximum after about 200 ms. Stimulus gaps induced a partial reset of the 40-Hz oscillations and a subsequent rebound, which again required 200 ms of time and resembled the time course of the onset response. Although the amount of partial reset decreased for shorter gap duration, the time interval for amplitude recovery was approximately the same for all gap types.

For quantifying the effects of the experimental conditions on the 40-Hz amplitude, we averaged the four response segments of 400-ms duration related to the stimulus onset and to the onsets of stimuli after each gap. Hilbert amplitudes of averaged 40-Hz responses are shown in Figure 5A,B for young and older

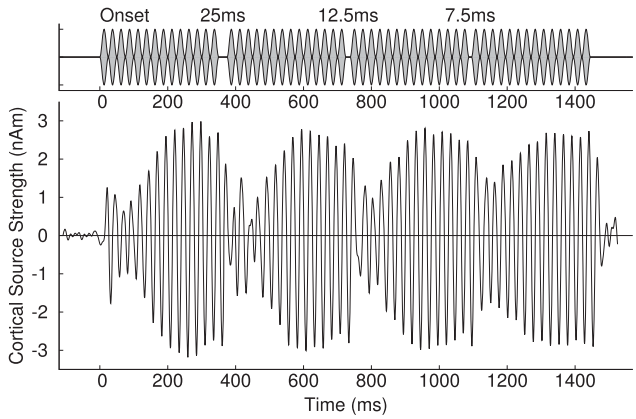


**Figure 4.** Grand-averaged 40-Hz responses to the stimulus onset and gaps of different lengths in the young group without masking. The stimulus with gaps of 25-ms, 12.5-ms, and 7.5-ms duration is shown on top. During the experiment, the gaps occurred in random order. The responses were averaged according to the gap duration and concatenated for this illustration in ordered fashion.

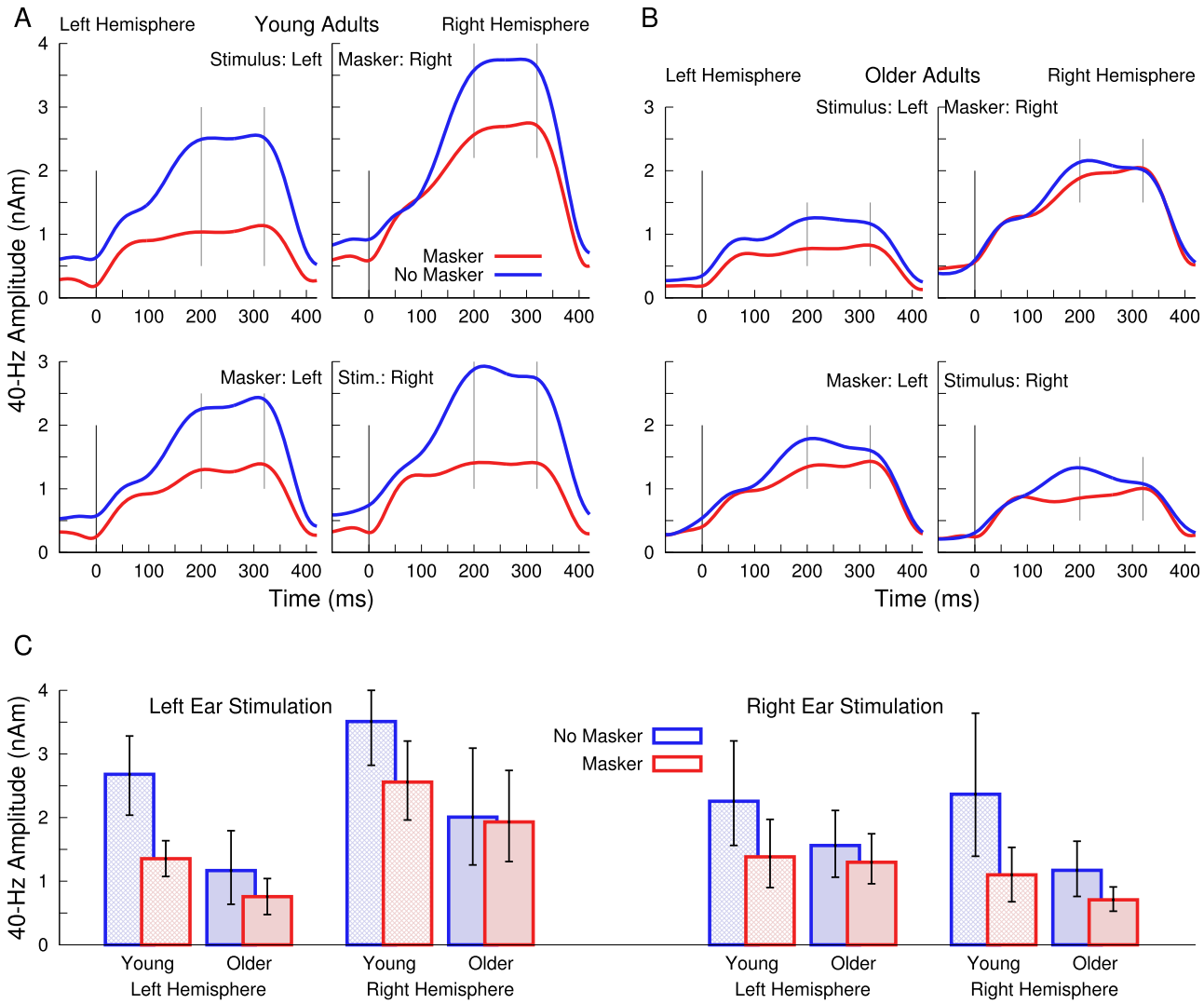


**Figure 5.** Time series of the Hilbert amplitudes of the 40-Hz responses observed in young (A) and older (B) participants, for monaural presentation of the stimulus to the left and right ear, recording from left and right auditory cortex, and presence or absence of the contralateral masker. C: The bar graphs show the mean 40-Hz amplitudes in the latency interval between 200 ms and 325 ms and the 95% CIs for the mean. The latency intervals for measuring the mean amplitudes are indicated with vertical lines in A and B.

participants, for left and right ear stimulation, and for recording from the left and right auditory cortices, with and without masking. Moreover, the mean amplitudes in the latency interval of steady oscillation between 200 ms and 325 ms are shown as bar graphs in Figure 5C together with error bars indicating the 95% confidence limits of the group means.

One noticeable feature in Figure 5A,B was that 40-Hz amplitudes were reduced under all experimental conditions when the contralateral masker was presented. However, the effect sizes of masking as well as the magnitudes of the amplitudes in general were remarkably different.

A repeated measures ANOVA with the between-subjects factor age (young vs. older) and within-subject factors masking (masking vs. quiet) and stimulation side (ipsilateral vs. contralateral) revealed main effect of age and masking. In mean, 40-Hz amplitudes were larger in the young group and without masking. Details of the statistical analysis are presented in Table 1A. Most importantly, an interaction between age and masking was evident because masking reduced the 40-Hz amplitudes significantly only in the young group. Also, 40-Hz amplitudes were larger in young compared to older adults only without masking, whereas no differences between age groups were significant when the masking sound was presented. Moreover, a main effect of the stimulation side was significant, with larger 40-Hz responses in the hemisphere contralateral to the stimulated ear. An interaction between the factors stimulation side and masking was significant, because the principle of larger contralateral responses was valid only under masking, whereas the monaural stimulus elicited similar response amplitudes in both hemispheres without masking.

The interaction between age and masking justified separate analyses for the age groups by repeated measures ANOVAs with the within-subject factors masking, ear (left vs. right), and hemisphere of recording. Details of the ANOVA results are summarized in Table 1B. The three main effects of masking (larger 40-Hz amplitude without masking), ear (larger responses with left ear stimulation), and hemisphere (larger responses in right auditory cortex) were significant in the young but not the older adults. An interaction between ear and hemisphere was significant in both age groups;

**Table 1.** *ANOVA Results for the 40-Hz Amplitudes*

**A.** Repeated Measures ANOVA with the Between-Subjects Factor Age (Young vs. Older) and Within-Subject Factors Stimulation Side (Contralateral vs. Ipsilateral) and Masking (Quiet vs. Contralateral Masking)

| | | |
|---|---|---|
| Between-subjects effect of age (young vs. older) | $F(1,22) = 5.16$ | $p = .033$ |
| Effect of masking (masking vs. no masking) | $F(1,22) = 29.9$ | $p < .0001$ |
| Interaction Age × Masking | $F(1,22) = 9.76$ | $p = .0049$ |
| Effect of masking in the young | $F(1,46) = 11.2$ | $p = .0016$ |
| Effect of masking in the older | $F(1,46) = 1.40$ | $p = .24$ (*n.s.*) |
| Effect of age with masking | $F(1.46) = 3.04$ | $p = .09$ (*n.s.*) |
| Effect of age without masking | $F(1,46) = 12.9$ | $p = .0008$ |
| Effect of stimulation side (contralateral vs. ipsilateral) | $F(1,22) = 56.7$ | $p < .0001$ |
| Interaction Stimulation × Masking | $F(1,22) = 5.37$ | $p = .030$ |
| Effect of contralaterality without masking | $F(1,46) = 1.72$ | $p = .197$ (*n.s.*) |
| Effect of contralaterality with masking | $F(1,46) = 14.5$ | $p = .0004$ |

**B.** Repeated Measures ANOVA with the Within-Subject Factors Ear of Stimulation, Masking, Hemisphere of MEG Recording, Separately for the Two Groups

| | Young | | Older | |
|---|---|---|---|---|
| Effect of masking | $F(1,11) = 28.1$ | $p = .0003$ | $F(1,11) = 4.4$ | $p = .071$ (*n.s.*) |
| Effect of hemisphere of MEG recording | $F(1,11) = 21.6$ | $p = .0007$ | $F(1,11) = 2.3$ | $p = .16$ (*n.s.*) |
| Effect of ear of stimulation | $F(1,11) = 6.49$ | $p = .0271$ | $F(1,11) = 0.9$ | $p = .36$ (*n.s.*) |
| Interaction Ear × Hemisphere | $F(1,11) = 38.6$ | $p < .0001$ | $F(1,11) = 27.5$ | $p = .0003$ |
| Effect of hemisphere with left ear stimulation | $F(1,46) = 8.96$ | $p = .0044$ | $F(1,46) = 8.57$ | $p = .0053$ |
| Effect of hemisphere with right ear stimulation | $F(1,46) = 0.05$ | $p = .8$ (*n.s.*) | $F(1,46) = 5.12$ | $p = .028$ |
| Interaction Ear × Masking × Hemisphere | $F(1,11) = 2.01$ | $p = .18$ (*n.s.*) | $F(1,11) = 7.7$ | $p = .018$ |
| Effect of masking, right ear stimulation, right hemisphere | | | $t(11) = 2.35$ | $p = .038$ |

however, the source for the interaction seems to be different. In the older group, a hemispheric difference was significant with right ear and left ear stimulation because response amplitudes were larger contralateral to the stimulated ear. In the young group, the principle of contralateral larger responses was offset by larger responses in the right hemisphere. Thus, no hemispheric difference occurred with right ear stimulation, whereas the laterality was strongly expressed with left ear stimulation. The interactions between stimulation ear and brain hemispheres can be observed clearly in the time series of Figure 5A,B, which also demonstrates that both effects were similar with and without masking in the young group. In the older group, the three-way interaction of Ear × Hemisphere × Masking was significant, because the effect of masking was significant in the right hemisphere with right ear stimulation only. Figure 5C also shows that, for the young participants, the 95% confidence intervals for the mean amplitude under masking did not include the mean without masking and vice versa, whereas in the older participants, this was the case for the right auditory cortex response with right ear stimulation only.

### Temporal Dynamics of 40-Hz Amplitude and Phase

The stimulus gaps induced a characteristic modulation of the 40-Hz amplitude, showing a sudden reset and a 200-ms interval of rebound. The AM gap resembled a brief delay in time, equivalent to a stepwise change in the phase of amplitude modulation. The phase of 40-Hz oscillations adjusted dynamically to the stimulus change. Notably, the temporal dynamics of the phase transition was different with and without masking. For the case of the shortest 7.5-ms gap, time series of the 40-Hz oscillations and time series of phase transitions are shown in Figure 6. In this figure, a 40-Hz sine wave was overlaid to the recorded oscillations as a visual reference, with the phase adjusted to the 250-ms to 350-ms latency interval. Comparison between the 40-Hz oscillations and the reference sine wave allowed identifying phase deviations from the mean phase in the steady-state interval. In case of masking, the phase of 40-Hz oscillation was readjusted within fewer than two cycles to the 7.5-ms step in time. In contrast, without masking, the phase entrainment was more complex: Immediately after the stimulus gap, the 40-Hz phase adjusted only partially and required another 200 ms of gradual alignment to the final steady-state phase. The phase delay

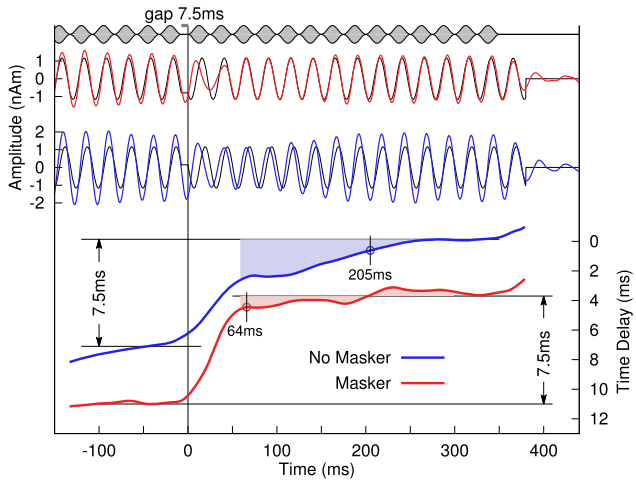


**Figure 6.** Time series of 40-Hz oscillations and phase transitions following a 7.5-ms gap in the AM stimulus. A reference sine wave (black line) was overlaid to the time series of the 40-Hz oscillations under masking (red) and without masking (blue). The phase of the reference sine wave was adjusted to the phase of oscillations in the 250-ms to 350-ms latency interval. In cases of masking, the 40-Hz oscillations adjusted quickly to the 7.5-ms time delay. Without masking, a quick phase adjustment occurred only partially, and another 200 ms of gradual phase change was required to complete the stimulus gap-induced time delay. Thus, the brain response under masking followed the stimulus changes with higher acuity than without masking. The lower panel shows the time courses of the phase transitions. The latencies of 64 ms under masking and 205 ms without masking, at which the phases reached 90% of the steady-state value, are marked with circles.

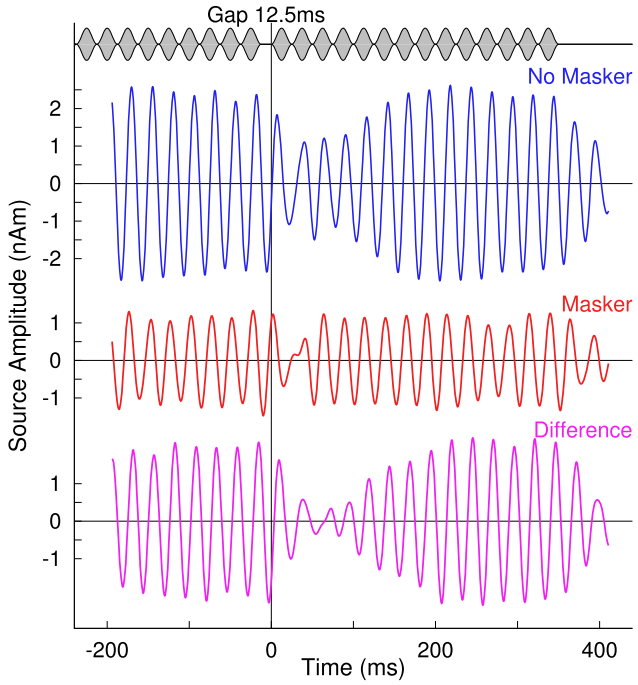


**Figure 7.** Two components of stimulus-induced 40-Hz oscillations. 40-Hz oscillations recorded with masking (red) showed a brief disruption after the stimulus gap**;** 40-Hz oscillations recorded in quiet without masking (blue) showed an additional signal increase over a 200-ms time interval. The response in quiet can be explained as the sum of the response obtained under masking (red) and the difference (magenta) between the MEG signals observed without and with masking.

was quantified by the latency at which 90% of the steady-state phase was reached, which was 64 ms with masking and 205 ms without masking (Figure 6). Apparently, under masking the phase dynamics of 40-Hz responses represented the stimulus with higher fidelity than when observed in quiet. A superior representation of the stimulus time course in presence of the masking noise may be seen as a paradoxical finding. One possible explanation is that the response in quiet contained an additional component of 40-Hz oscillation, which was less strictly phase-locked to the stimulus and was suppressed in noise. Figure 7 illustrates such concept of multiple components of the 40-Hz response. By subtracting the 40-Hz oscillations obtained under masking from the response observed without masking, we separated the 40-Hz response into two components, one obligatory response, which was elicited even under the masking condition, and an additional component, which occurred without masking only. Both components of 40-Hz oscillations showed characteristic differences in their temporal dynamics. The first component reacted quickly to changes in the stimulus and was tentatively termed the sensory component. The second component showed a complete reset of the amplitude after the stimulus gap and a 200-ms time interval of rebound. Because this temporal dynamic is consistent with earlier observations of temporal integration (Ross et al., 2002), we termed this component of 40-Hz oscillations the binding component.

### Effect of Age on 40-Hz Oscillations

We analyzed whether the multiple components of 40-Hz responses were different in young and older listeners. Grand-averaged 40-Hz responses for both age groups are summarized in Figure 8. The first difference between age groups was that the 40-Hz responses in the older adults were delayed by 3.0 ms compared to young adults (Figure 8A). This delay in phase was constant over time, and did not affect the amplitude dynamics in the response differently between the groups. The amount of observed delay is compatible to previous findings in older adults in the middle latency response (Woods & Clayworth, 1986), which is closely related to the 40-Hz response. Therefore, for the following figures, we advanced the responses of older adults by 3.0 ms for visual comparison of the response time courses.

A striking finding was the close similarity of the time series in the case of contralateral masking (Figure 8C). Besides slightly larger amplitude in the younger group, older adults reacted as quickly as young to the stimulus change induced by the 12.5-ms gap. The response waveforms followed the stimulus envelope almost perfectly and recovered from the perturbation within a single cycle. This was a strong contrast to the time series observed without masking, specifically in the young group (Figure 8B), which showed a steep decrease in the response amplitude followed by a slow rebound with full recovery of the amplitude after 200 ms. Such modulation of the 40-Hz amplitude seems less pronounced in the older adults. We calculated the time series of differences between the response without masking and with masking (Figure 8D), which showed similar temporal patterns for both age

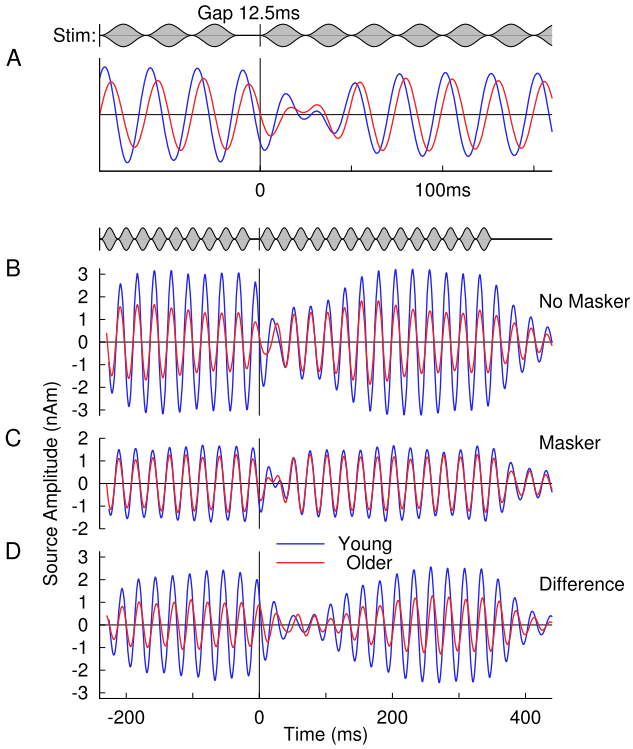


**Figure 8.** 40-Hz responses in young and older listeners. The time series were averaged across hemispheres and left and right ear stimulation. A: Time series obtained with masking reveal a delay in the responses of older listeners. For better comparison of amplitudes, the response time series of the older participants in B–D were advanced by 3.5 ms. B: Without masking, larger 40-Hz amplitudes were observed in young adults compared to older. C: Time series of both groups resembled each other and showed only little disruption after the stimulus gap in the masked condition. D: The difference waves between conditions, interpreted as synchronous oscillation in the binding circuit, were larger in the young compared to older participants.

groups. While the responses in both age groups were characterized by the 200-ms lasting recovery after the gap, amplitudes were noticeably smaller in older adults. For further analysis, we compared the 40-Hz responses, which were observed under masking, with the additional activity observed in the no-masking condition. We statistically examined whether this latter component (i.e., the difference between the masking and no-masking conditions) was affected by age.

A statistical analysis of the two components of the 40-Hz oscillations, performed with an ANOVA with the between-subjects factor age and the within-subject factor component (sensory, binding), revealed main effects of age, $F(1,10) = 5.10$, $p = .047$, and component, $F(1,10) = 9.28$, $p = .012$, and most importantly an interaction between both factors, $F(1,10) = 5.15$, $p = .046$. The reason for the interaction between age and component was that the amplitudes of the sensory component of the 40-Hz responses, as measured with masking, were not different between age groups, $F(1,22) = 1.87$, $p = .18$, *n.s.*, whereas the binding components, measured as the differences between responses in quiet and with masking, were different between groups, $F(1,22) = 6.33$, $p = .020$. In the group mean, the amount of 40-Hz binding oscillations was equal to 84%, 95% CI [67, 103] of the amplitude in the sensory component in the young group, whereas it was only 42%, 95% CI [22, 67] in the older group.

### Correlation with Speech-in-Noise Performance

The correlation analysis between the amplitudes of the two components of 40-Hz oscillations and the performance in speech-in-noise understanding showed that the 40-Hz amplitude under masking was not significantly correlated with speech-in-noise loss (Figure 9A). However, the second component was strongly correlated with the performance in the Quick-SIN test, $R^2 = .68$, $F(1,22) = 41.1$, $p < .0001$. The regression was performed on the 40-Hz amplitude increase between observations without and with masking, normalized to the 40-Hz amplitude measured under masking (Figure 9B). Testing the regression separately for each group showed significant correlation in the older adults, $R^2 = .87$, $F(1,11) = 54.9$, $p < .0001$, but not in the young, $R^2 = .01$, $F(1,11) = 0.12$, *n.s.* A subsequent analysis of covariance (ANCOVA) revealed effects of group, $F(1,17) = 9.17$, $p = .008$, 40-Hz amplitude, $F(1,17) = 7.2$, $p = .0157$, and a Group × 40-Hz Amplitude interaction, $F(1,17) = 7.3$, $p = .0154$. No such group differences were found for the 40-Hz amplitude under masking.

While spectral acuity, measured with detection of a mistuned harmonics, was correlated with speech-in-noise loss, no correlation was found between spectral acuity and the amplitudes of the two types of 40-Hz oscillations combined or separately for the age groups ($F < 1.0$ in all cases).

### Correlation Between 40-Hz Response and P2

Previous studies suggested that the P2 response is related to identification of auditory objects. We tested whether P2 amplitudes were correlated with amplitudes of the 40-Hz responses in order to contribute to this discussion. Linear regression analysis showed that, without masking, the P2 peak amplitudes were correlated with the 40-Hz amplitudes, $R^2 = .237$, $F(1,44) = 13.3$, $p = .0007$ (Figure 10). When each group was examined separately, the correlation between P2 and 40-Hz amplitudes was significant in the young group, $R^2 = .31$, $F(1,23) = 9.70$, $p = .005$, and showed a tendency in the older group, $R^2 = .18$, $F(1,18) = 3.84$, $p = .066$; however,

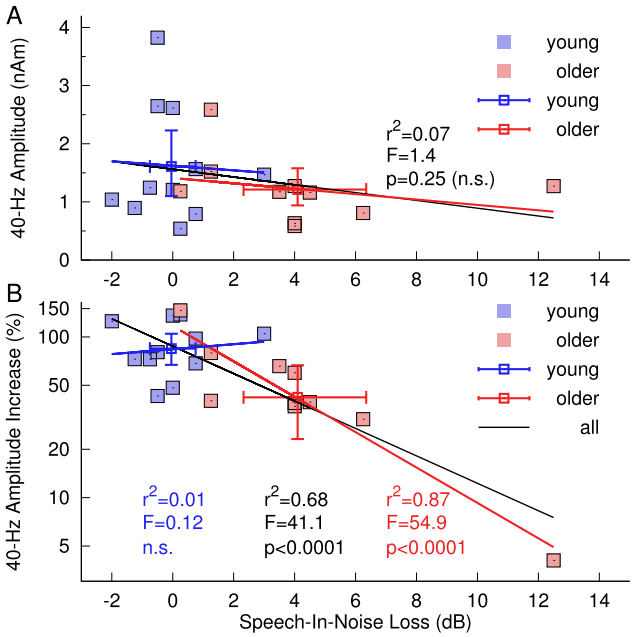


**Figure 9.** Correlation between the components of 40-Hz oscillations and performance in speech-in-noise understanding. A: The amplitude of the sensory component, observed with central masking, was not significantly different between the age groups. B: The amplitude of the 40-Hz binding component, expressed as the percent increase over the non-masked response, was different between groups and correlated with speech understanding in noise. The speech-in-noise loss equals the increase in signal-to-noise ratio, which a listener would require for normal speech-in-noise perception. All error bars denote the 95% CIs for the group mean.

the ANCOVA did not reveal a difference between the regression slopes, $F(1,39) < 0.1$, *n.s.* With masking, which attenuated both the P2 and the 40-Hz response, no significant correlation between the amplitudes was found. Under the masking condition, the N1 amplitudes were only weakly correlated with the 40-Hz responses, $R^2 = .09$, $F(1,22) = 4.47$, $p = .04$, while no correlation was evident without masking.

## Discussion

The current study revealed two main findings. First, contralateral multitalker babble noise attenuated auditory evoked cortical 40-Hz oscillations, and the effect size was larger in young than older adults. Second, the time courses of the 40-Hz responses followed the stimulus more precisely with noise than without noise. While the finding that noise attenuated the response amplitude seems intuitively understandable, the further results need more careful consideration. Questions are: Why was the effect of noise more pronounced in young, while older adults have greater difficulties with listening in noise? and Why was a more fuzzy response observed without noise than with noise? Taking into account the previous literature on the role of gamma oscillations for perception, we will discuss how our results can be related to changes in central auditory processing, contributing to speech-in-noise understanding deficits in aging. The discussion is furthermore supported by our finding that noise affected the amplitude of the auditory evoked P2 wave at 200-ms latency but not the earlier P1 and N1 waves, considering that the sequence of auditory evoked responses represents

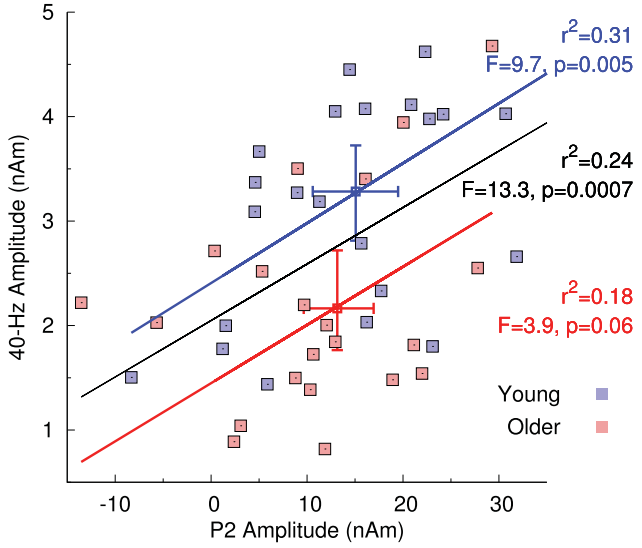


**Figure 10.** Correlation between P2 amplitudes and amplitudes of 40-Hz oscillations in the binding network for young adults (blue), older adults (red), and all participants (black). Error bars indicate grand mean P2 and 40-Hz amplitudes and the 95% CIs in both age groups.

a hierarchy of central auditory processing, each stage of which is differently affected by noise and aging.

### Hearing Performances in Young and Older Adults

Although older participants showed only mildly elevated hearing thresholds at high frequencies normal for their age (Cruickshanks et al., 1998), for speech understanding they required 3.5 dB larger signal-to-noise ratio (SNR) than the young. This may be seen as a small quantity; however, considering that a speaker raises her or his voice by no more than 2.0 dB above noise level (Plomp, 1977), 3.5 dB SNR loss constitutes an impairment rather than an inconvenience. While normal hearing listeners understand speech under such adverse conditions (Bronkhorst, 2000), the SNR loss excludes older people from conversations in noise, leading to social isolation and withdrawal (Hilton & Huang, 2008). Speech intelligibility degrades as much as 20% when the SNR decreases by a single decibel (Duquesnoy, 1983).

The Quick-SIN test (Killion et al., 2004) required repeating five-word sentences and thus involved working memory. With working memory deficits, participants would have missed some words at high SNR; however, no age differences were found at the largest SNR of 25 dB. Nonetheless, older participants missed some words at SNR of 10–15 dB, which may speak for the contribution of functional deficits beyond signal detection. With respect to temporal and spectral acuity, some older adults performed as well as the young, and the behavioral measures were characterized by overlapping distributions with slightly separated centroids between age groups. In summary, the age groups seemed to be more different on the level of perception than on sensation.

### Auditory Evoked Responses

We found that contralateral noise affected P2 but not N1 amplitudes, and that the reduction of P2 was smaller in aging. These findings are consistent with previous literature: Using ipsilateral masking, in which stimulus and noise interacted physically at cochlear level, it was observed that N1 and P2 responses were reduced in older age (McCullagh & Shinn, 2013). It could be that N1 reduction in their report was related to masking at the cochlear level, which was absent in our study using contralateral noise. With respect to age-related P2 difference, ipsilateral noise attenuated the P2 amplitude more in older adults than in young (Crowley & Colrain, 2004), suggesting that the P2 wave is sensitive to age-related changes. When using contralateral masking as in our study, clear effects of age on evoked responses in the latency range of 200 ms and beyond were observed with EEG (Bertoli, Smurzynski, & Probst, 2005). It is important to note that in their study only P2 was attenuated, but not the earlier N1, which is consistent with our findings. Under the view that the N1 response reflects sensation (Näätänen & Picton, 1987), the finding that contralateral masking did not affect the N1 amplitude is consistent with only marginal elevation of the behavioral sensation threshold (Mills et al., 1996; Zwislocki, 1972). Our study provided new observations about the P2 response: While P2 amplitudes in quiet were larger in young adults, contralateral noise modulated the P2 amplitude more in young than older adults. Thus, P2 amplitudes in presence of noise were no more different between age groups. With the better behavioral performances in the young, this could be interpreted as the younger brain having a wider range of processing capabilities and thus being able to handle concurrent noise more easily. The auditory evoked N1 response was not attenuated in aging (Chao & Knight, 1995). Our finding of slightly larger N1 amplitudes in older adults is consistent with stronger auditory cortex activation in a recent fMRI study (Profant et al., 2015), which had been related to compensatory mechanisms in aging.

For further interpreting of the P2 results, it is important to consider what type of auditory processing is performed in the 200-ms latency range. The auditory system performs a complex spectro-temporal analysis involving a hierarchy of processing steps within the auditory pathways (Felleman & Van Essen, 1991; Rauschecker, 1998). Näätänen and Winkler (1999) proposed that the N1 response reflects the initial storage of sensory information, which is present at the level of auditory cortex, but not yet accessible for subsequent conscious perception. This is reinforced by reaction time studies, showing that one- or two-syllable words are accessible about 200 ms after word onset (Marslen-Wilson, 1987). At this latency, the neural representation of an auditory object is established and now accessible for conscious processing. P2 has been suggested as indicating successful completion of this process (Kuriki, Ohta, & Koyama, 2007). Then again, reduced resources for this step of central auditory processing may suggest that aging and noise affect object formation and perception.

A P2 amplitude increase had been observed between subsequent recordings (Ross & Tremblay, 2009), and the effect may exist for long retention time (Tremblay, Inoue, McClannahan, & Ross, 2010). However, in the current study, P2 amplitudes were not significantly larger in the second session with right ear stimulation. Also, no reports of changes in the 40-Hz amplitude between subsequent recordings are known. Therefore, we consider that MEG recording with left and right ear stimulation in separate sessions did not constitute a confounding effect on the reported results.

### Aging-Related Changes on Auditory Steady-State Responses

We found differences in 40-Hz responses between young and older listeners. Neurobiological changes in the auditory system commence early in life and increase gradually over the lifetime as shown, for example, with cochlear synaptic loss in mice, contributing to gradually increasing sensation loss (Sergeyenko, Lall, Liberman, &

Kujawa, 2013). Thus, aging may affect perception of amplitude modulation and generation of 40-Hz ASSR, which in turn could partly explain our findings about changes in the 40-Hz amplitude. Previous literature reported that young and older adults improve in speech-in-noise understanding when the masker is amplitude modulated compared to steady noise (Grose, Mamo, & Hall, 2009). While young adults showed larger release from masking, those benefits vanished for fast speech, suggesting that speech understanding in older adults was not affected by temporal processing per se but depended on the availability of speech cues for further interpretation. The same study showed equal ASSR amplitudes for young and older listeners at 32-Hz modulation frequency and reduced ASSR amplitudes in the older only at significantly higher modulation frequency of 128 Hz. The latter result is consistent with the report of equal 40-Hz ASSR amplitudes in young and older adults, while differences between ages became evident at modulation rates above 100 Hz (Purcell, John, Schneider, & Picton, 2004). Moreover, 40-Hz ASSRs at 520 Hz and 4000 Hz were reduced only in older adults with high frequency hearing loss or when hearing loss was simulated with masking in young listeners (Boettcher, Madhotra, Poth, & Mills, 2002). Temporal dynamics of 40-Hz ASSR were introduced as sensitive indicators for effects of age on sound localization based on interaural time relation (Ross, 2008; Ross et al., 2002; Sergeyenko et al., 2013). Although binaural hearing was already significantly affected in midlife (Ross, Fujioka, Tremblay, & Picton, 2007), ASSR amplitudes were not different between age groups. In summary, the 40-Hz ASSR amplitude seems more consistent over the adult lifetime than one would expect given strong evidence for aging-related changes at all levels of the auditory system. Still, a comparison of absolute amplitudes across age groups could be potentially misleading because multiple effects of changes over lifetime could compensate each other. Importantly, the main outcome measures in our study were not absolute amplitude changes across age groups but within-group differences of responses under different experimental conditions.

### 40-Hz Oscillation in a Corticothalamic Binding Network

We reported previously the 200-ms lasting onset of 40-Hz oscillations and suggested its function as an indication of auditory temporal integration (Ross et al., 2002). The same temporal dynamics were observed in this study after a gap occurred in the stimulus and corroborate previous findings that a change in the stimulus environment induced a reset of the 40-Hz oscillation followed by reconfiguration of binding (Ross, 2008; Ross et al., 2005; Ross & Pantev, 2004). The new findings about the effects of contralateral noise provide more insight into possible neural mechanisms underlying the generation of 40-Hz oscillations.

A neural circuitry for generation of 40-Hz gamma oscillations in a corticothalamic network has been documented in detail (Destexhe, Contreras, & Steriade, 1998; Jones, 2002; Llinás et al., 2002). A simplified schematic of the neural circuitry (Figure 11) may help to interpret the findings of our study. Forty-Hz oscillations are generated in loops of reciprocal connections between large pyramidal cells in cortical layers IV and V and nuclei of the thalamus (Jones, 2009). The properties of rapid firing interneurons, located at the place of distal termination of the thalamic projection, determine the oscillatory behavior of the circuits, which are narrowly tuned in the 40-Hz range (Steriade, Timofeev, Dürmüller, & Grenier, 1998). Multiple functionally distinct circuits are spatially overlaid and coupled through synchronous oscillations (Jones, 2009). It has been discussed that those 40-Hz oscillations bind together the fragments of a complex stimulus (Lisman, 1998). Figure 11 illustrates two corticothalamic loops, one representing the incoming auditory stimulus, termed the specific sensory circuit (left) and a second loop (right) related to a higher-order stimulus representation, termed the nonspecific binding circuit (Jones, 2001). The MEG signal is mainly generated by intracellular current flow resulting from the propagation of postsynaptic discharges along the apical dendrites of the pyramidal cells in layers IV and V (Lopes Da Silva & Van Rotterdam, 1982). The overlap of neural population makes it particularly challenging for neuroimaging to resolve neural oscillations in the specific or the nonspecific circuits, which also occur simultaneously and phase-locked in time. However, our experimental paradigm of probing the gamma network with noise helped dissociate these two types of activities.

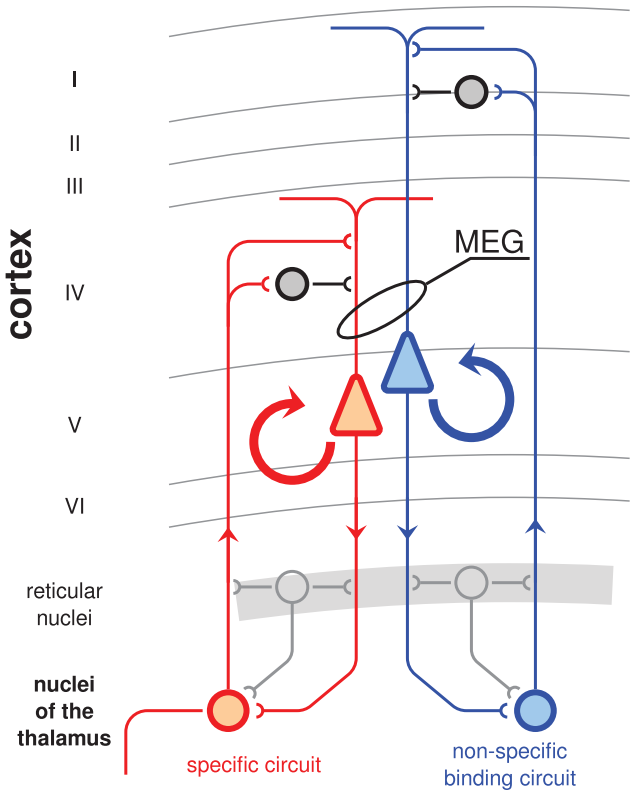


**Figure 11.** Thalamocortical circuitry for generation of 40-Hz oscillations. Reciprocal connections between large pyramidal cells (triangles) in cortical layers IV and V and nuclei of the thalamus form local oscillators tuned to the 40-Hz range. Multiple circuits representing the sensory input (specific circuit) and higher-order representations (nonspecific binding circuit) are spatially overlaid. Functional binding between specific and nonspecific circuits is realized through synchronous oscillations. The MEG records current flows in the apical dendrites of the pyramidal cells resulting from postsynaptic excitation.

### Contralateral Masking of 40-Hz ASSR

The earlier findings that contralateral noise attenuated 40-Hz ASSR by no more than half of the unmasked amplitude (Galambos & Makeig, 1992) had been corroborated subsequently (Kawase et al., 2012; Maki, Kawase, & Kobayashi, 2009; Okamoto, Stracke, Ross, Kakigi, & Pantev, 2007). Those studies also demonstrated that the effects of the contralateral noise are only marginal on the amplitudes of brainstem responses and the cortical N1 wave as well as behavioral threshold shifts, which were typically shown as less than 2 dB. Our results that contralateral multitalker babble

noise had little effect on the N1 amplitude and partially attenuated the 40-Hz response are consistent with those reports. In sum, those behavioral and electrophysiological findings support our interpretation that the component of 40-Hz oscillation that remained in noise is related to auditory sensation. In our study, contralateral noise may have affected synchrony for coupling between specific sensory and nonspecific circuits. Therefore, with noise, we recorded gamma oscillations from the specific circuit only. Without noise, the MEG detected the sum of synchronous 40-Hz oscillations in both circuits. Finally, with the difference operation, we separated oscillations in specific and nonspecific networks. Thus, our interpretation of the two components of 40-Hz oscillation as being related to sensory processing and perceptual binding, respectively, seems compatible with the already established neural mechanism underlying generation of gamma oscillations.

With this study, we emphasize the role of 40-Hz oscillations for sensory and perceptual binding, for which previously only animal studies provided the link between neural mechanisms and mass activity. While the MEG picks up activity from the cortical level of a cortico-thalamocortical network, responses from the thalamic counterpart have been recorded with and without masking in rats (Martin, West, & Bedenbaugh, 2004). Masking changed the timing of neurons in the medial geniculate body. Thus, upstream auditory networks received a scrambled pattern of the acoustical input and were not able to meaningfully interpret the neural activity. This finding supports our hypothesis that central masking affects the synchrony in thalamocortical networks. The interpretation that noise interferes with neural timing but does not suppress the primary sensory response is consistent with the experience that people can hear a speaker in noise but cannot understand the meaning.

We reported previously the effect of contralateral multitalker noise on auditory 40-Hz oscillations (Ross, Miyazaki, & Fujioka, 2012). Another recent study (Usubuchi et al., 2014) showed that white noise modulated 40-Hz steady-state responses; however, the effect was smaller at 20 Hz, emphasizing that concurrent noise interacted specifically with a 40-Hz network. We demonstrated that an equivalent neural mechanism exists in the somatosensory system, for which concurrent finger stimulation interrupted 40-Hz oscillations but did not modulate the 20-Hz oscillations (Ross, Jamali, Miyazaki, & Fujioka, 2013). Those findings may indicate the specific role of 40-Hz oscillations for perception.

For the amplitudes of 40-Hz oscillations and the P2 wave, we found interactions between the effects of age and masking with noise reduced the responses more in young than in older adults. This does not mean that younger adults were more vulnerable to noise. The temporal dynamics of amplitude and phase of 40-Hz oscillations following the perturbation induced by the stimulus gap provided a more differentiated view that the 40-Hz oscillations consists of two components. Almost identical responses were found in young and older adults under contralateral masking and led to the interpretation that the amount of masking-related modulation indicates an additional response component, which is available in silence.

That 40-Hz oscillations were of similar amplitude in young and older adults reinforces that sensory information is preserved with high temporal acuity in the auditory cortex in aging. The difference between age groups became significant only when analyzing the attenuation of 40-Hz oscillations with contralateral masking. Forty-Hz oscillations in the sensory binding network were smaller in older adults, suggesting reduced resources and less efficient sensory integration. That aging limits available brain resources has been mainly discussed for cognitive function; however, similar mechanisms seem to apply to perception (Lindenberger & Ghisletta, 2009).

### Correlations Between Brain Responses and Speech-in-Noise Performance

We found a significant correlation between speech-in-noise loss and increase in 40-Hz oscillations when contralateral masking was removed. However, there was no significant correlation with the 40-Hz amplitude under masking. Correlation between speech-in-noise loss and 40-Hz amplitudes was significant in the older adults but not in the young, and this group difference was significant. The finding of a correlation between speech-in-noise loss and the 40-Hz amplitude specific for older adults supports the hypothesis of a functional relation between both. We interpreted the statistical interaction between age and response amplitude for both the P2 response and the 40-Hz oscillations as an indicator of limited resources or less efficient processing in the older group. The correlation between P2 amplitudes and 40-Hz amplitudes supports the hypothesis of functional relation between the neural mechanisms underlying both responses. The correlation should not be interpreted as redundancy that P2 and 40-Hz oscillation reflect a single process; following the principle of parsimony, it seems more likely that the responses reflect two different aspects of a common process, which calls for further research for clarification. Our P2 results are consistent with recent findings of larger P2 amplitudes in high-performing compared to poorly performing elderly listeners (Getzmann, Wascher, & Falkenstein, 2015), which had been interpreted as indicating the ability to allocate resources for compensatory mechanisms.

While spectral acuity as measured with detection of a mistuned harmonics was correlated with speech-in-noise loss, neither 40-Hz amplitudes nor the P2 were correlated with spectral acuity. Both changes in spectral acuity with likely more peripheral cause and changes in central auditory processing contribute to speech-in-noise deficits. However, peripheral and central effects may develop independently as suggested from a recent animal study (Ouda et al., 2015) .

### Aging and Neural Synchrony

Recent work discovered that neural synchrony at the level of the auditory brainstem is important for successful speech-in-noise perception (Anderson, Parbery-Clark, Yi, & Kraus, 2011). Those findings and the neural mechanism we described in this study are complementary. It is unlikely that speech-in-noise deficits in the complex auditory system have a single isolated cause. All subsystems from the auditory periphery to cognition are strongly interacting. One encouraging finding from studies of neural synchrony at the brainstem level is that experience (e.g., musicianship) or training can improve synchrony (Parbery-Clark, Strait, Hittner, & Kraus, 2013) and may preserve synchrony in aging as reflected in superior speech-in-noise perception (White-Schwoch, Carr, Anderson, Strait, & Kraus, 2013). Whether plasticity in the corticothalamic binding system exists is still unknown. The 40-Hz oscillations in the binding system rely strongly on GABAergic interneurons. Recently, plasticity for the human adult GABAergic system has been proposed (Méndez & Bacci, 2011).

In addition to previous findings, our study emphasizes an important aspect of cortical synchrony: it seems that aging does not generally reduce synchrony but interacts differently with functional subsystems. It is still a question for future research as to why sensory integration becomes less efficient with aging.

While it is widely accepted that gamma oscillations are involved in binding, the controlling mechanisms that lead to binding of acoustical elements into a spoken word are still beyond current knowledge.

## Conclusion

Our MEG study investigated whether gamma oscillations could reflect the neural mechanism contributing to impaired speech-in-noise perception in older age. We separated stimulus evoked gamma oscillations into two components. Noise interacted with the efficacy of sensory integration in the central auditory system, and likely impaired the higher-order representation of an auditory object for perception. Gamma oscillations in the binding network were strongly affected by contralateral noise and were reduced in older age, indicating that neural resources for sensory integration are limited in aging.

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