

# Short-term habituation of auditory evoked potential and neuromagnetic field components in dependence of the interstimulus interval

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**Abstract** Repeated auditory stimulation results usually in a response decrement of event-related potential components. In the current study, we investigated the impact of the interstimulus interval (ISI) on the response decrement. Healthy subjects were stimulated with trains of five tones, with an ISI of 600, 1,200, or 1,800 ms within the trains. Auditory evoked potentials (AEP) were recorded from the vertex, as well as neuromagnetic auditory evoked fields (AEF) from the left temporal region. Stimulus repetition led to a response decrement for the studied AEP components (N100 and P200) and AEF components (N100m and P200m). However, for all used ISIs, there was no further response decrement after the 2nd stimulus. The ISI affected only the magnitude but not the kind of the response decrement. No evidence for a gradual response decrement was revealed at any used ISI. This finding indicates that the response decrement is probably due to the refractoriness of cell assemblies involved in the generation of AEP and AEF components, rather than the result of a genuine habituation process. The finding questions habituation as the mechanism behind short-term decrements of AEP/AEF components.

**Keywords** Electroencephalography (EEG) · Auditory cortex · Magnetoencephalography (MEG) · Sensory gating

## Introduction

Auditory evoked potentials (AEPs) have now been studied for 70 years. The first report on the vertex potential as a response to auditory stimulation is dated back to 1939 (Davis 1939). Later studies revealed that this vertex potential consists of several components, which might be subdivided according to their latency and polarity (Picton et al. 1974). The N100 represents the largest AEP component and has been associated with cognitive processes like memory functions (Sams et al. 1993) or stimulus classification (Pantev et al. 1989). The N100 is succeeded by the P200, whose function is less well understood (Crowley and Colrain 2004).

AEP amplitudes show a negative exponential dependence on the interstimulus interval (ISI), as shown first for the N100-P200 peak-to-peak amplitude (Davis et al. 1966). In association with that, amplitudes of AEP components are diminished by repetition of identical tone stimuli in trains. No decrement is observed when the ISIs within the trains are very long ( $\geq 10$  s) (Ritter et al. 1968; Budd et al. 1998), suggesting that the decreased AEP amplitudes to repeated stimuli result from the refractory period of the neural cell assemblies generating the AEP components. Based on that, one would propose that such a response decrease depends on intrinsic qualities of involved neural cell assemblies and, therefore, is not related to learning processes. Of note, the relation of refractoriness on the level of ERP components and of refractoriness on the level of single neurons is poorly understood as yet (Wehr and Zador 2005).

In contrast, others have conceptualized the diminished ERPs to repeated stimuli as habituation (Fruhstorfer et al. 1970). Habituation is regarded as a primitive form of learning (Sokolov 1960; Thompson and Spencer 1966),

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because repeated stimulation results in an adaption of behavior. In their seminal paper, Thompson and Spencer (1966) defined nine criteria of habituation. Among others, the decrease to repeated stimuli is assumed to be a negative exponential function of the number of stimulus presentations (Thompson and Spencer 1966, p. 18). Such a gradual decrease is indeed found for different kinds of response behaviors across various species (see for illustration Fig. 2 in Christoffersen 1997). Other criteria of habituation, as defined by Thompson and Spencer (1966), encompass e.g. the response recovery with a change in stimulation or a dishabituation following such a change. On the neural level, habituation has been linked to synaptic depression (e.g. Simons-Weidenmaier et al. 2006). However, also other neural mechanisms, like tonic inhibitory input from higher central areas, have been proposed to be involved in habituation (Krasne and Teshiba 1995; for review Christoffersen 1997).

Refractoriness and habituation are not necessarily fully exclusive models for explaining the response decrement to repeated stimuli, but there are different kinds of response decreases as expected outcomes on the basis of the two models, as proposed first by Budd et al. (1998). If the amplitude decrease was due to refractoriness, reduction should stabilize after the first repetition, because the response strength would solely depend on the ISI preceding the repeated stimulus. In contrast, habituation should, as outlined, be associated with a more gradual decrease (Thompson and Spencer 1966; Picton et al. 1976).

Previous electroencephalography (EEG) and magnetoencephalography (MEG) studies investigating the short-term decrement of AEPs and their neuromagnetic counterparts to repeated auditory stimuli did not reveal uniform results: some studies showed a completed decrease after the 2nd stimulus (EEG: Bourbon et al. 1987; Barry et al. 1992; Soininen et al. 1995; Budd et al. 1998; Määttä et al. 2005; Rosburg et al. 2004, 2006; Grau et al. 2007; Fuentemilla et al. 2009; MEG: Lammertmann et al. 2001; Rosburg 2004; Sörös et al. 2006, 2009), while other studies showed a further continuing decrease (EEG: Ritter et al. 1968; Fruhstorfer et al. 1970; Öhman and Lader 1972; Woods and Elmasian 1986; MEG: Sörös et al. 2001).

The reason for this discrepancy between studies is not clear. Since some of the studies which found a gradual decrease used longer ISIs (Ritter et al. 1968; Fruhstorfer et al. 1970; Öhman and Lader 1972), we have previously proposed that the response decrease could possibly be modulated by the ISI within the stimulus trains, with longer ISIs making it more likely to observe a gradual decrease (Rosburg 2004). Such an influence of the ISI on the response behavior would be in concordance with the hypothesis of Loveless (1983) that temporal uncertainty is a key factor underlying fast habituation as well as temporal

recovery. However, previous studies varying the ISI (1, 3, 10 s) showed mixed results (Fruhstorfer et al. 1970; Budd et al. 1998).

Therefore, the current study re-addressed this issue and tested whether increasing the length of the ISI within the stimulus train has an impact on the nature of the response decrease. For practical reasons, we focused on a lower range of ISIs (0.6, 1.2, 1.8 s), because we wanted to study the same subjects within a single session at all three ISIs. Such an approach avoids a potential impact of inter-subject variability, when different subject groups are assigned to particular ISIs, and a potential impact of inter-session variability, when the same subjects are studied at different levels of ISIs, but in multiple sessions.

We recorded the cortical responses to repeated auditory stimulation simultaneously by EEG and MEG. The AEP components N100 and P200 are assumed to be generated by various brain regions (N100: Näätänen and Picton 1987; P200: Crowley and Colrain 2004). In contrast, MEG is sensitive only for sources with a tangential orientation to the head surface (Cohen and Cuffin 1983). Thus, the neuromagnetic auditory evoked field (AEF) components (N100m, P200m) reflect activity of a specific subset of N100 and P200 generators. The generators of the AEF components are usually located in the vicinity of Heschl's Gyrus (N100m: Näätänen and Picton 1987; P200m: Crowley and Colrain 2004). Combined EEG/MEG measurements provide a more complete picture of cortical activity elicited by auditory stimulation than one method alone, as e.g. shown by studies on sensory gating (Clementz et al. 1997; Thoma et al. 2003). This is to our knowledge the first study using combined EEG/MEG in order to investigate the short-term decrement to repeated auditory stimulation with trains of stimuli.

Taken together, the current study aimed to investigate the response decrement of AEP/AEF components to repeated auditory stimulation at different ISIs, in order to differentiate between habituation and refractoriness as underlying mechanisms. We hypothesized that the response decrement would be modulated by the ISI within the trains: We expected to observe a gradual decrease as indicator for habituation at the longest ISI, but not at the shortest ISI.

## Methods

### Participants

The study group consisted of 18 healthy subjects (9 men), with an average age of 24.8 years (range 21–27). All participants were students or staff members of the University of Jena and were free of any apparent psychiatric or

neurological disorder. Subjects gave written consent after being thoroughly informed about the purpose and content of the study. Students received a financial compensation of 15 € for their participation. The study was approved by the ethics committee of the University of Jena.

### Stimulation

Subjects were stimulated monaurally in three blocks. Stimulation in each block consisted of trains of 5 tones with 50-ms duration each (including 5 ms rise and fall time) and a pitch of 1,000 Hz, presented at 75 dB sound pressure level. All trains were separated by 6,000 ms. Only the ISI within the trains varied between the blocks (600, 1,200, 1,800 ms). The order of blocks was counterbalanced within the total study. As a lower signal-to-noise ratio was expected at shorter ISIs, the number of averages was higher for these blocks: In the 600-ms condition, blocks consisted of 150 trains, in the 1,200-ms condition of 90 trains, and in the 1,800-ms condition of 75 trains. The total recording time was about 60 min. The subjects were instructed to avoid carefully any movements during the recordings, as well as to keep their eyes open and fixated to a point at the wall of the recording chamber. Tonal stimulation was not associated with any kind of task.

Subjects were lying on their right body side on a vacuum cushion, with the head resting on a separate cushion. The head cushion had an aperture, connected to a funnel-shaped ending of a plastic tube used for delivering the computer-generated sine tones. The commercial software Presentation, version 9.12 (Neurobehavioral Systems, Albany, CA, USA), was used for stimulation.

### Recording

Neuromagnetic recordings were carried out with a 31 channel neuromagnetometer system (Philips Medical Systems, Hamburg, Germany) in a shielded chamber (Vacuumschmelze, Hanau, Germany). The sensor array (diameter about 150 mm) was centered over the left temporal lobe, contralaterally to the stimulated ear. In order to achieve a good positioning of the dewar, the AEF component N100m was recorded before the experiment. Subjects were stimulated with 64 tones, delivered with an ISI between 800 and 1,800 ms. After a possible correction of the dewar, the blocks with train stimuli were recorded.

In order to ensure that subjects did not move during the recordings, the head position was determined by means of 5 orthogonal coils of 5 mm diameter affixed to the head. These coils were localized before and after each recording block. The positions of the five coils in relation to three anatomical landmarks (left and right preauricular points and nasion) were digitized before and after the recording

sessions by an ISOTRAK II system (Polhemus Inc., Colchester, VT, USA). These reference points were employed in order to match the MEG data with high-resolution magnetic resonance images (MRIs) performed on a 1.5 T GYROSCAN (Philips Medical Systems, Hamburg, Germany; recording parameters: 3D-Flash-sequence producing 256 sagittal images of 1-mm slice thickness with a  $256 \times 256$  matrix covering the entire head). The MRIs were needed for the source reconstruction.

In addition to MEG, EEG was recorded from 3 electrodes (Fz, Cz, Pz) with sintered Nihon-Kohden silver-silver chloride electrodes. The reference electrode was affixed to the right earlobe. Eye movements and blinks were recorded with two pairs of additional electrodes, one pair positioned below and above the left eye and one pair at the right and left outer canthus. The sampling rate for all electrophysiological recordings (EEG, EOG, MEG) was 1,000 Hz.

### Data analysis

The five tones in a train are labeled in the following as S1–S5. Auditory evoked potentials and neuromagnetic field components were averaged for each tone (S1–S5) and each train (600/1,200/1,800 ms) separately. All EEG data were processed by means of the software program Brain-Vision Analyzer, V1.04 (Brain Products GmbH, Munich, Germany). EEG data were high-pass filtered (0.3 Hz, 12 dB) and segmented in trials of 700 ms length, including 100 ms as pre-stimulus baseline. EOG artifacts were corrected with the implemented algorithm of Gratton et al. (1983). After a baseline correction, all segments with activity  $>75 \mu\text{V}$  were rejected as artifacts. Here, we just report on data collected at Cz. Data were filtered from 1 to 40 Hz (12 dB/octave). Peak amplitudes and latencies were obtained for the N100 and P200. The N100 was assumed to peak between 70 and 140 ms and the P200 between 150 and 240 ms. AEP peaks were measured with respect to baseline (–100 to 0 ms).

MEG data were analyzed by the software package CURRY V4.6 (Neuroscan, El Paso, TX, USA). Data were segmented in trials of 700 ms length, including 100 ms as pre-stimulus baseline. Trials with more than 3,000 fT in any MEG channel or with more than  $150 \mu\text{V}$  in EOG channels were rejected as artifacts. Remaining trials were averaged and filtered with a Wiener filter (Daubechies 12) and a third-order Butterworth filter. As the EEG data, MEG data were filtered from 1 to 40 Hz for the analysis of the N100m and P200m. In addition, any common trend found in all MEG channels was removed and data were baseline corrected. Peak mean global field power (MGFP) values and latencies were obtained for the N100m, as well as for the P200m.

## Source reconstruction

In addition to MGFP values, the decrement of neuromagnetic field responses was studied by analyzing the dipole moments. For fitting dipoles, a singular value decomposition was performed and only components with an SNR >1 were included. A single moving dipole and a realistic volume conductor model representing the inner surface of the skull (boundary element model) were used for the source reconstruction. Dipole moments were extracted at all peak maxima (N100m, P200m). A dipole was accepted as solution of the inverse problem only if it was located in the region of the auditory cortex. In addition, a dipole had to explain at least 70% of the measured field for the N100m and P200m to S1. Even using a more liberal criterion for the P200m, the dipole reconstruction turned out to be problematic for this latency range and dipoles could be fitted only in a small portion of subjects ( $n = 4$ ). Since the analysis of the dipole moments revealed results very similar to those obtained by the analysis of MGFP values, only the latter is reported here, because the analysis of MGFP values was based on more comprehensive data.

## Statistics

Amplitude and latency values of AEP and AEF components were subjected to a two-way analysis of variance (ANOVA) with TONE (S1 vs. S2 vs. S3 vs. S4 vs. S5) and ISI (600 vs. 1,200 vs. 1,800 ms) as factors for repeated measurement. This analysis was assumed to provide information about the amplitude and latency behavior for repeated stimulation in general. As the amount of the response suppression from the 1st to the 2nd stimulus is known to depend on the ISI (with sharper decreases for shorter ISIs), significant TONE  $\times$  ISI interactions were an expected finding for this ANOVA. Post hoc pairwise comparisons between S1 and following stimuli were conducted by an ANOVA with TONE (S1 vs. S2/S3/S4/S5) and ISI as factors for repeated measurement.

Since the main target of the study was to show a decline after the 2nd stimulus in dependence of the ISI, data were subjected to a second ANOVA with TONE (S2 vs. S3 vs. S4 vs. S5) and ISI (600 vs. 1,200 vs. 1,800 ms), thus excluding the responses to the 1st stimulus. Within this ANOVA, data were also tested for linear trends for the factor TONE. A significant main effect of TONE would indicate a general systematic variation of the AEF and AEP components by tone repetition after the 1st stimulus. In case of a gradual decrease, a significant linear trend for the factor TONE was expected. If longer ISIs were associated with a gradual decrease and shorter ISIs were not, significant TONE  $\times$  ISI interactions and significant linear trends at the longest ISI should be observed. A Greenhouse–Geisser correction was

performed where necessary, as indicated by the citation of  $\epsilon$  values. For statistical comparisons, the level of significance was set at  $P < 0.05$ .

## Results

EEG data were successfully obtained in all subjects. MEG data of one subject had to be excluded due to technical failure. Exemplary EEG and MEG data are depicted in Fig. 1.

### Repetition effects from S1 to succeeding stimuli

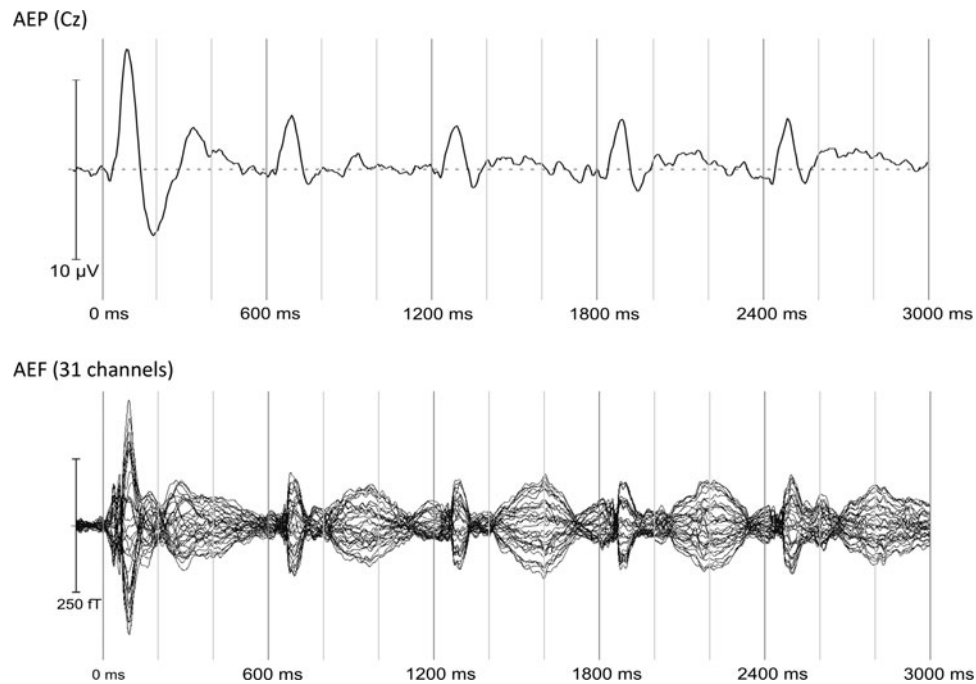
EEG data: The amplitudes of both analyzed AEP components decreased after S1 (N100:  $F_{4,68} = 57.453$ ,  $P < 0.001$ ,  $\epsilon = 0.498$ ; P200:  $F_{4,68} = 8.426$ ,  $P = 0.006$ ,  $\epsilon = 0.300$ ). Post hoc pairwise comparisons confirmed larger AEP amplitudes in response to S1, when compared to the AEP amplitudes in response to all succeeding stimuli (all  $F_{1,17} > 8.234$ ,  $P < 0.011$ ). In addition, the latencies of both AEP components decreased after S1 (N100:  $F_{4,68} = 13.510$ ,  $P < 0.001$ ; P200:  $F_{4,68} = 14.032$ ,  $P < 0.001$ ). Post hoc pairwise comparisons confirmed significant shorter N100 and P200 latencies in response to S1, when compared to the N100 and P200 latencies in response to S2–S5 (all  $F_{1,17} > 13.421$ ,  $P < 0.002$ ). For descriptive group data, see Tables 1 and 2.

MEG data: Similar to the EEG data, the amplitudes of the N100m and P200m were diminished by stimulus repetition from S1 to the succeeding stimuli (N100m:  $F_{4,64} = 132.928$ ,  $P < 0.001$ ,  $\epsilon = 0.467$ ; P200m:  $F_{4,64} = 11.320$ ,  $P < 0.001$ ,  $\epsilon = 0.473$ ). Post hoc pairwise comparisons revealed larger AEF amplitudes in response to S1 than to other stimuli (all  $F_{1,16} > 11.237$ ,  $P < 0.004$ ). Significant latency differences were found for the P200m ( $F_{4,64} = 3.575$ ,  $P = 0.031$ ,  $\epsilon = 0.595$ ), while latency differences for the N100m were not significant ( $F_{4,64} = 2.125$ , n.s.). Of note, also the P200m latency decrease from S1 to S2 did not reach significance in the post hoc testing ( $F_{1,16} = 2.030$ , n.s.), possibly indicating a gradual latency decrease. For descriptive group data, see Tables 1 and 2.

### Repetition effects from S2 to S5

Data were screened for gradual latency and amplitude decreases by analyzing the AEPs and AEFs in response to S2–S5 separately. The  $F$  values and  $P$  values of this comparison are summarized in Table 3.

EEG data: The AEPs to S2–S5 looked virtually the same (Fig. 2). There was no indication for a further gradual decrease in AEP amplitudes after S2 across ISIs: Factor TONE was not significant for the N100 and P200



**Fig. 1** Exemplary EEG (*top*) and MEG (*bottom*) data of one individual in the 600-ms condition (filtered 1–40 Hz). For better orientation, time intervals of 200 ms are marked by *vertical lines*. The *upper trace* depicts the AEP, as recorded at Cz, with negative values plotted upwards. A N100-P200 complex in response to each of the five stimuli can be seen. The AEP amplitudes decreased from the 1st

to the 2nd stimuli, but not thereafter. MEG was recorded over the left temporal cortex, covering incoming and outgoing field gradients. Therefore, MEG data were characterized by a spread into positive and negative amplitude values. The AEF amplitudes decreased from the 1st to the 2nd stimuli, but not thereafter

**Table 1** The mean amplitudes ( $\pm$ SD) of the AEP components [in  $\mu$ V] and AEF components [in fT] to each stimulus of the train, for each ISI separately

	ISI (ms)	S1	S2	S3	S4	S5
EEG						
N100	600	-7.3 (2.3)	-3.6 (1.6)	-3.4 (1.2)	-3.4 (1.7)	-3.2 (1.4)
	1,200	-8.3 (2.9)	-5.3 (2.6)	-5.1 (2.4)	-5.4 (2.7)	-5.3 (2.3)
	1,800	-8.6 (2.9)	-6.4 (2.2)	-6.7 (2.6)	-5.9 (2.2)	-6.9 (2.1)
P200	600	5.2 (4.9)	2.1 (1.0)	1.8 (1.3)	1.9 (1.3)	1.9 (1.4)
	1,200	6.0 (3.8)	3.3 (1.7)	3.3 (1.3)	3.4 (1.5)	3.6 (1.8)
	1,800	6.8 (5.3)	5.1 (2.2)	5.1 (1.8)	5.0 (2.2)	4.8 (2.2)
MEG						
N100m	600	704.7 (128.3)	270.6 (105.6)	276.5 (97.0)	311.6 (90.7)	316.7 (101.3)
	1,200	785.0 (250.5)	348.3 (168.6)	386.4 (173.5)	396.2 (163.2)	392.7 (157.8)
	1,800	794.4 (198.8)	536.6 (211.8)	534.4 (226.1)	494.2 (209.2)	531.4 (188.3)
P200m	600	343.5 (146.9)	231.3 (127.3)	163.5 (70.4)	160.7 (75.6)	192.4 (74.3)
	1,200	334.0 (141.2)	242.1 (118.5)	266.3 (140.9)	288.4 (127.4)	254.0 (104.7)
	1,800	347.3 (157.9)	312.6 (167.1)	322.4 (166.5)	329.7 (155.0)	304.5 (157.4)

Note the little variation within the data of each row from S2 to S5, but the increasing amplitude values with increasing ISI

amplitudes, and polynomial trend analysis of the N100 and P200 amplitudes revealed no significant linear trend for the TONE factor either. Similarly, N100 and P200 latencies were hardly affected by tone repetitions after S2. However, a linear trend over tone positions 2–5 approached significance for P200 latencies ( $P = 0.073$ ), with decreasing

latencies from S2 to S5. TONE  $\times$  ISI interactions did not reach significance for any EEG variable.

MEG data: Amplitudes of AEFs to S2–S5 showed little variation (Fig. 3). There were no significant TONE effects on the N100m and P200m amplitudes. Polynomial trend analysis of the N100m and P200m amplitudes revealed no

**Table 2** The mean latencies ( $\pm$ SD) of the AEP and AEF components [in ms] to each stimulus of the train, for each ISI separately

	ISI (ms)	S1	S2	S3	S4	S5
EEG						
N100	600	96.7 (9.1)	90.0 (12.3)	91.4 (15.0)	88.4 (10.5)	88.4 (12.2)
	1,200	97.4 (9.8)	86.6 (9.3)	85.9 (7.9)	89.1 (8.8)	88.4 (9.5)
	1,800	99.6 (10.6)	89.2 (7.9)	91.7 (8.1)	91.6 (9.0)	92.5 (8.0)
P200	600	175.2 (19.1)	171.6 (29.9)	160.6 (23.0)	156.7 (27.2)	158.9 (25.7)
	1,200	186.4 (26.9)	159.1 (25.0)	161.9 (26.4)	164.8 (26.3)	160.2 (28.9)
	1,800	186.4 (22.7)	174.7 (31.2)	169.8 (25.6)	173.3 (25.4)	169.8 (23.5)
MEG						
N100m	600	95.4 (9.1)	95.8 (18.1)	93.7 (19.2)	93.2 (16.0)	93.5 (15.3)
	1,200	94.2 (8.3)	91.8 (12.0)	91.5 (10.1)	90.4 (11.0)	91.0 (11.6)
	1,800	95.0 (8.0)	93.0 (10.1)	93.2 (9.6)	92.8 (9.1)	92.9 (10.5)
P200m	600	182.9 (38.9)	177.9 (36.1)	178.6 (41.5)	173.3 (43.0)	163.8 (36.0)
	1,200	179.6 (37.0)	173.1 (35.8)	170.8 (38.0)	174.0 (38.3)	173.6 (41.0)
	1,800	176.7 (36.4)	173.5 (35.4)	172.9 (35.9)	167.9 (31.5)	170.7 (34.1)

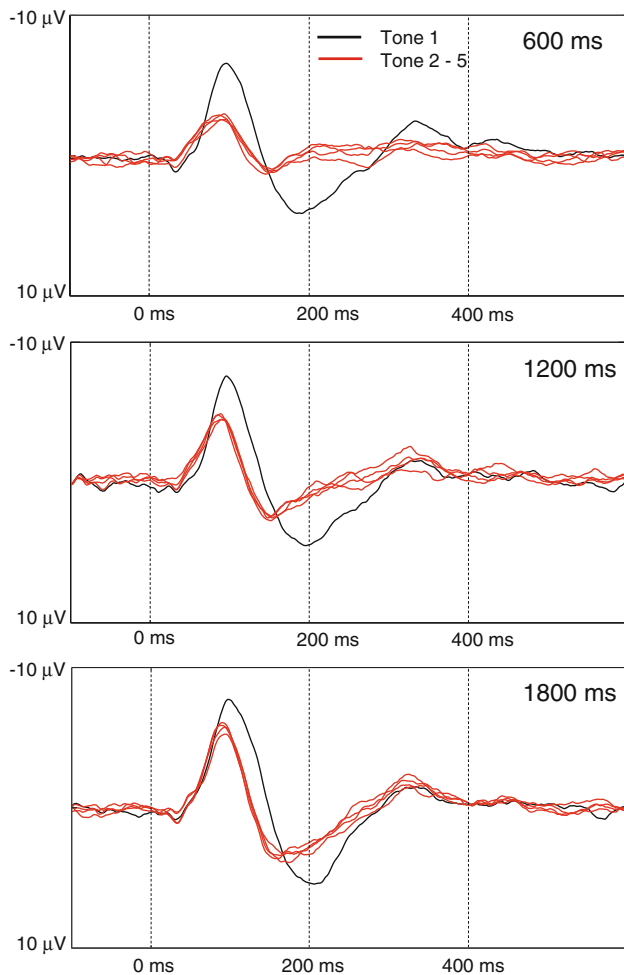
**Table 3** The  $F$  values and  $P$  values of the ANOVA with TONE (S2 vs. S3 vs. S4 vs. S5) and ISI (600 vs. 1,200 vs. 1,800 ms) as within-subject factors

	TONE	TONE Linear trend	ISI	TONE $\times$ ISI
Amplitudes				
EEG				
N100	$F_{3,51} = 0.807$	$F_{1,17} = 0.102$	$F_{2,34} = 29.221$	$F_{6,102} = 2.105$
	n.s.	n.s.	$P < 0.001$	n.s.
P200	$F_{3,51} = 0.072$	$F_{1,17} = 0.139$	$F_{2,34} = 43.307$	$F_{6,102} = 0.436$
	n.s.	n.s.	$P < 0.001; \epsilon = 0.681$	n.s.
MEG				
N100m	$F_{3,48} = 1.757$	$F_{1,16} = 3.805$	$F_{2,32} = 13.601$	$F_{6,96} = 1.764$
	n.s.	n.s.	$P < 0.001$	n.s.
P200m	$F_{3,48} = 0.615$	$F_{1,16} = 0.537$	$F_{2,32} = 11.786$	$F_{6,96} = 3.116$
	n.s.	n.s.	$P < 0.001$	$P = 0.030; \epsilon = 0.548$
Latencies				
EEG				
N100	$F_{3,51} = 0.373$	$F_{1,17} = 0.606$	$F_{2,34} = 2.266$	$F_{6,102} = 0.977$
	n.s.	n.s.	n.s.	n.s.
P200	$F_{3,51} = 1.912$	$F_{1,17} = 3.663$	$F_{2,34} = 2.217$	$F_{6,102} = 2.487$
	n.s.	n.s.	n.s.	n.s.
MEG				
N100m	$F_{3,48} = 0.993$	$F_{1,16} = 1.625$	$F_{2,32} = 1.016$	$F_{6,96} = 0.324$
	n.s.	n.s.	n.s.	n.s.
P200m	$F_{3,48} = 1.982$	$F_{1,16} = 6.242$	$F_{2,32} = 0.066$	$F_{6,96} = 1.902$
	n.s.	$P = 0.024$	n.s.	n.s.

$P$  values  $> 0.05$  are listed as n.s. (non-significant)

significant linear trend for the TONE factor either. A significant TONE  $\times$  ISI interaction was found for the P200m amplitude, but not for the N100m amplitude. However, trend analyses of P200m amplitudes for each ISI separately gave no evidence for a linear decrease

(all  $F_{1,16} < 1.926$ , n.s.). The N100m latencies did not vary systematically between S2 and S5, neither as effect of TONE alone nor in interaction with ISI. In contrast, a significant linear trend of P200m latencies for the TONE factor was found, indicating decreasing P200m latencies from S2 to S5.

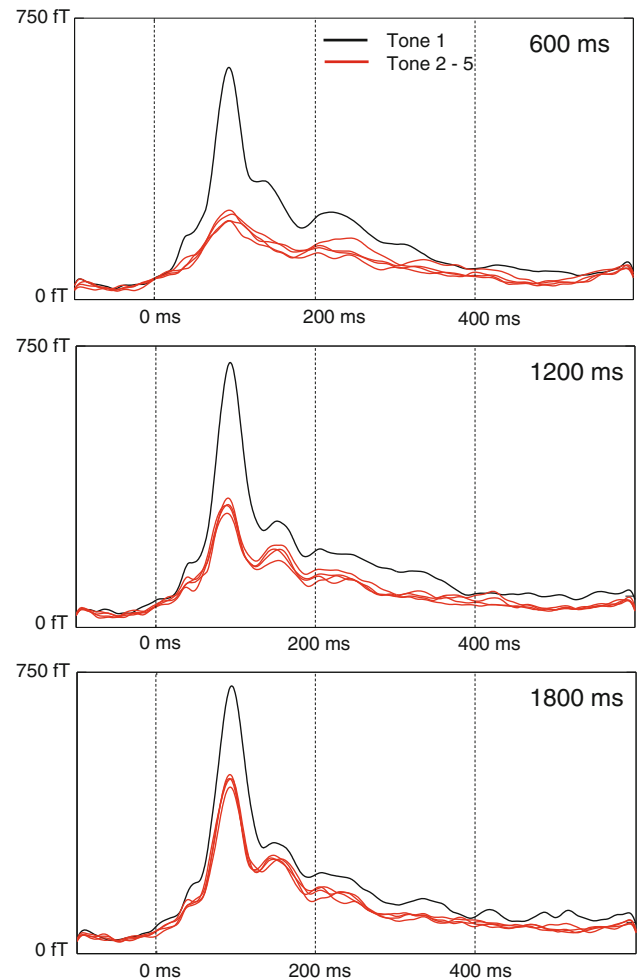


**Fig. 2** Grand average EEG data for the three conditions at Cz (*top row* ISI = 600 ms; *middle row* ISI = 1,200 ms; *bottom row* ISI = 1,800 ms). Data were filtered from 1 to 40 Hz. The AEP in response to the 1st stimulus of a train is shown as *black line*; the AEPs to the 2nd to 5th stimulus are shown as *red/grey lines*. The amplitudes of the AEP components to the 1st stimulus clearly surmounted the amplitudes in response to the 2nd to 5th stimulus, with little variation within the latter

### ISI effects

The conducted ANOVA revealed also strong effects of ISI on amplitude values.  $F$  values and  $P$  values are found in Table 3. Both AEF and AEP amplitudes increased significantly with increasing ISI. In contrast, latencies were not affected by ISI.

Visual inspection of the data suggested that the AEP/AEF amplitudes to the 1st stimulus could possibly be influenced by the ISI within the trains, with larger amplitudes for larger ISIs. This was not an expected observation, since S1 tones were preceded by the same ISIs in all conditions. In order to test for possible effects, AEP/AEF amplitudes in response to the 1st stimulus of each train were compared between conditions. However, the results of this ANOVA



**Fig. 3** Grand average MEG data for the three conditions (*top row* ISI = 600 ms; *middle row* ISI = 1,200 ms; *bottom row* ISI = 1,800 ms). The depicted data represent the MGFP. Data were filtered from 1 to 40 Hz. The AEF in response to the 1st stimulus of a train is shown as *black line*; the AEFs to the 2nd to 5th stimulus are shown as *red/grey lines*

did not corroborate the visual impression: S1 N100 and P200 differences between conditions were not significant (N100:  $F_{2,34} = 2.969$ , n.s.; P200:  $F_{2,34} = 2.145$ , n.s.). The S1 N100m and P200m did not differ between conditions either (N100m:  $F_{2,32} = 1.586$ , n.s.; P200m:  $F_{2,32} = 0.142$ , n.s.).

### Discussion

The findings of the current study can be summarized as follows: stimulus repetition led to a response decrement of the investigated AEP (N100, P200) and AEF components (N100m, P200m). The ISI as independent variable affected the magnitude of the response decrements, with stronger

decreases for shorter ISIs. However, evidence for a gradual amplitude decrease could not be observed at any ISI. Of all analyzed variables, only the P200/P200m latencies showed a significant or close to significant gradual decrease.

Recent AEP and AEF studies revealed conflicting results with regard to the response decrease after several stimulus repetitions: many studies showed a response decrement completed after the first repetition (Barry et al. 1992; Bourbon et al. 1987; Fuentemilla et al. 2009; Grau et al. 2007; Määttä et al. 2005; Rosburg 2004; Rosburg et al. 2004, 2006; Soininen et al. 1995; Sörös et al. 2006, 2009; but Woods and Elmasian 1986), but at longer ISIs a gradual response decrease appeared to be more likely (Ritter et al. 1968; Fruhstorfer et al. 1970; Öhman and Lader 1972; but Budd et al. 1998). This potential impact of ISI was tested in the current study, by varying the ISI within the stimulus train.

However, at all tested ISIs, the response decrement was completed with the 1st repetition, for both EEG and MEG recordings. Thus, we could not confirm our hypothesis that a gradual response decrement becomes more likely at longer ISIs. The findings of the current study are in line with those of Budd et al. (1998), who also reported a lack of gradual AEP amplitude decreases at different ISIs (1, 3, 10 s). Both the current study and the study of Budd et al. (1998) are not supportive for the hypothesis of Loveless (1983) that temporal uncertainty is a key factor underlying fast habituation as well as temporal recovery. Following this hypothesis, increasing ISIs (but also using variable ISIs) would make the occurrence of auditory events less predictable and should result in larger cortical ERP responses. Some previous studies varying the predictability of auditory events using fixed vs. variable ISIs revealed increased ERP amplitudes for variable ISIs, thus have been supportive for the hypothesis (Rothman et al. 1970; Öhman et al. 1972; but Nelson et al. 1969; Nelson and Lassman 1977).

Across ISIs, we found no evidence for a gradual amplitude decrease either. The lack of any gradual decrease suggests that refractoriness (and not habituation) represents the major mechanism behind the response decrease, as previously also proposed by Budd et al. (1998). With other words, the reduced amplitudes of the analyzed AEP/AEF components are sufficiently explained by the shorter ISI within trains, when compared to the ISI between trains. Decreasing AEP and AEF amplitudes with decreasing ISIs is a well-established finding (e.g. Davis et al. 1966; Hari et al. 1982; Rojas et al. 1998). In line with that, we found the magnitude of the response decreases from the 1st to succeeding stimuli to be larger for shorter ISIs.

Current EEG and MEG recordings revealed similar response decrements and, thus, provided converging results. With other words, the here described findings did

not depend on the used recording technique. As outlined in the introduction, the AEP components N100 and P200 are assumed to reflect summed activity from various brain regions, while the AEF components N100m and P200m reflect activity of a specific subset of generators. Consequently, the response decrement could not a priori be assumed to be similar for AEP and AEF components. Indeed, EEG and MEG recordings sometimes provide diverging results (e.g. Clementz et al. 1997).

If refractoriness is the major mechanism behind the response decrease observed in stimulus repetition experiments like the current one, how do we have to interpret occasional reports of gradual decreases? Aside from assuming spurious findings, we think there are two conceivable explanations for gradual decreases: (1) when using very short ISIs, the AEPs/AEFs of succeeding stimuli might overlap. The observed gradual decrease in the study of Sörös et al. (2001, ISI = 220 ms) could result from such an overlap. Furthermore, it could also be the consequence of a temporal integration process occurring 200–300 ms after stimulus onset, with sound sequences falling into this so-called temporal window of integration being coded as unitary events (Cowan 1984). In line with that assumption, the N100/N100m amplitudes were found to be enhanced (and not further decreased) for shorter ISIs < 400 ms (Loveless et al. 1989; Budd and Michie 1994; Loveless et al. 1996). (2) Gradual decreases could possibly also be due to attention: Attention effects are rather difficult to control in this kind of stimulus repetition experiments, since the longer intervals without stimulation between stimuli trains are an inherent part of the experimental design. From dichotic listening experiments, there is ample evidence that selective attention can increase the N100 (Hillyard et al. 1973; Näätänen et al. 1981; Hackley et al. 1990; Woldorff and Hillyard 1991). We have recently shown that stimulus repetition effects can also be influenced by attention: In a paired-click experiment, subjects were instructed to direct their attention to the occurrence of the 2nd click. The AEP to the attended 2nd click was characterized by an underlying negativity, when compared to unattended stimulus repetitions (Rosburg et al. 2009a). We interpreted this negativity as so-called processing negativity (PN), which is usually observed in dichotic listening experiments when contrasting the ERPs to attended and unattended stimuli (Näätänen et al. 1981). In case that subjects pay attention to the beginning of stimulus trains and attention declines over time, this could in principle result in a gradual decrease in the N100/N100m amplitudes. However, for this potential confound, it should be stressed that in stimulus repetition experiments subjects are usually explicitly instructed not to attend to the stimuli.

Favoring the idea of habituation as underlying process for the response decrease, one could assume that an



underlying PN that increases in strength toward the end of the train could counterbalance a further N100/N100m amplitude decrease after the 2nd stimulus and, thus, conceal a gradual decrease. This could possibly happen in case subjects paid particularly attention to stimuli at the end of the train. However, for the currently obtained data, we regard this scenario as unlikely. An underlying PN would not only affect the N100/N100m but also the P200/P200m, albeit in the reverse direction. Since both N100/N100m and P200/P200m amplitudes remained stable after the first stimulus, there is no evidence that unwanted attention effects had an impact on the current findings.

The current study did not attempt to decompose the AEP/AEF signals into independent components and to analyze the response decrement of these independent components. In a recent study using the technique of independent component analysis (ICA), Grau et al. (2007) reported that some independent components peaking in the N100 latency range were completely suppressed by stimulus repetition. This was particularly true for frontally generated components, in line with anecdotic reports of intracranially recorded frontal N100 activity (see Fig. 1c in Rosburg et al. 2005).

Decomposing N100 activity into independent components and locating their generating structures appears to be a useful attempt to analyze effects of stimulus repetition in more detail, since the N100 and other AEP components are assumed to be generated by multiple brain regions (Näätänen and Picton 1987). In contrast, the N100m can sufficiently be explained by a single source in or close to Heschl's gyrus. In the current study, the decrease in both the N100m MGFP and the N100m dipole moment (data not shown) was completed with the first stimulus repetition. A similar finding had been reported in an own previous study (Rosburg 2004).

In other previous studies, we investigated the response decrements to repeated auditory stimulation by means of intracranial recordings. Intracranial ERPs primarily reflect locally generated activity. In these studies, recordings from posterior lateral surface of the superior temporal gyrus revealed no evidence for a gradual decrease in N100 activity either (Rosburg et al. 2004, 2006). Taken together, studies analyzing independent components (Grau et al. 2007), invasive studies (Rosburg et al. 2004, 2006), and studies using source reconstruction (Lammertmann et al. 2001; Rosburg 2004) did not reveal evidence that habituation contributes to the short-term decrements of AEP/AEF components to repeated stimuli.

In addition to decreased AEP/AEF amplitude, stimulus repetition led to decreased latencies of the AEP components N100 and P200 and of the AEF component P200m. The decreasing latencies of AEP components as result of repeated stimulation fit well to the existing body of

literature (N100: Bourbon et al. 1987; Budd et al. 1998; Rosburg 2004; Määttä et al. 2005; Rosburg et al. 2006; Fuerst et al. 2007; P200: Budd et al. 1998; Fuerst et al. 2007). In contrast to EEG studies, MEG studies did not reveal uniform repetition effects for the N100m latency (Lammertmann et al. 2001; Sörös et al. 2001; Rosburg 2004; Sörös et al. 2006, 2009). Of note, stimulus repetition was found to have no impact on the latency of intracranially recorded N100 activity (Rosburg et al. 2004, 2006).

As a surprising finding of the current study, the P200/P200m latencies showed a gradual decrease after S2. To our knowledge, an ongoing latency decrease as a result of repeated stimulation has not been described before. Since habituation refers to decreased response strength and not to changes in response speed, we think it is more reasonable to assume that this effect reflects a perceptual priming process than to interpret the gradual decrease in P200/P200m latencies as evidence for habituation. However, further studies are warranted to specify the functional significance of the gradual latency decrease as consequence of repeated stimulation.

Although the current findings fit well to the majority of previous findings, some limitations of the current study need to be named. We recorded only left-hemispheric AEFs because, when the study was conducted, only a 31-channel MEG system was at hand. However, at present, it would be rather speculative to assume systematic differences between left- and right-hemispheric short-term decrements of AEF components. To our knowledge, only one whole-head MEG study on the response decrement of the N100m has been conducted so far. This study showed an N100m decrement completed with the first stimulus repetition both for left-hemispheric and for right-hemispheric data (Lammertmann et al. 2001).

Furthermore, we did not test ISIs > 1,800 ms. Thus, based on the current study, we cannot exclude the possibility that a gradual decrease would have become apparent when using longer ISIs between the stimuli in the train. However, designs using rather slow presentation rates might be particularly prone to attention effects. Subjects stimulated with single tones at long ISIs often exhibit a P300 even when no task is associated with these stimuli, possibly indicating that attentional resources are engaged under these conditions (Mertens and Polich 1997). In this context, the impact of temporal uncertainty on the response decrease (Loveless 1983) warrants further investigation, with designs using a mixed presentation of trains with different ISIs rather than a blocked one.

Finally, we would like to stress that the current findings do not imply that habituation is of no relevance at all for the cortical processing of repeated stimuli. On the level of auditory receptor neurons, a gradual decline in response strengths with repeated stimulation was reported and

interpreted as “sensory habituation” (Givois and Pollack 2000). For EEG/MEG recordings with continuous auditory stimulation, a decrement of AEP/AEF components was reported, which continued over time periods of minutes and hours (EEG: May et al. 1994; Picton et al. 1976; Roeser and Price 1969; MEG: Rosburg et al. 2000, 2002). The long-term decrement of AEP and AEF components cannot be explained by refractoriness, except we assume that refractoriness itself is modulated by the continuous stimulation, and might possibly reflect a habituation process. However, it has yet to be tested whether other criteria defining habituation are fulfilled for the long-term decrement of AEP and AEF components (Thompson and Spencer 1966). To our knowledge, so far it has only been shown that stimulus change results in a response recovery (Rosburg et al. 2002), while other criteria await their testing. In the current experiment, a long-term decrement of AEP and AEF components was observed as well (data not shown).

Understanding the mechanisms behind repetition effects on AEP/AEF components will provide large benefit for the interpretation of findings on clinical populations. Alterations of repetition effects have been described among others for patients with schizophrenia as deficient sensory gating (for review: Bramon et al. 2004), for chronic alcoholics (Fuentemilla et al. 2009), or migraine patients (for short review: Giffin and Kaube 2002). Recent sensory gating studies using the paired-click paradigm provided evidence that an impaired suppression of the cortical response could be related to a deficient encoding of the unrepeated click and, thus, might not indicate an inefficient filtering of sensory information (Hong et al. 2004, 2008; Rosburg et al. 2009b).

## Conclusion

The current study found the response decrement of AEP and AEF components to be completed with the first stimulus repetition, irrespective of the used ISI. We interpret this finding as evidence that refractoriness is the major mechanism behind the short-term decrement of AEP and AEF components after repeated stimulation.

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