Clinical Neurophysiology 127 (2016) 397–408

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The response decrease of auditory evoked potentials by repeated stimulation – Is there evidence for an interplay between habituation and sensitization?

Timm Rosburg [a,*], Peter Sörös [b]

[a] Department of Psychology, Experimental Neuropsychology Unit, Saarland University, D-66041 Saarbrücken, Germany
[b] Department of Neurology, University of Lübeck, D-23538 Lübeck, Germany

ARTICLE INFO

Article history:
Accepted 25 April 2015
Available online 8 May 2015

Keywords:
Auditory evoked potentials
N100
Short-term decrements
Habituation
Sensory gating
Refractoriness

HIGHLIGHTS

- We investigated the decrease of auditory evoked potentials by stimulus repetition.
- Trial selective averaging of auditory evoked potentials revealed no evidence that their response decrease after repeated stimulation is modulated by an interplay of habituation and sensitization.
- Refractoriness is considered a more appropriate account for the response decrease than habituation.

ABSTRACT

Objectives: To assess whether the response decrement of auditory evoked potentials (AEPs) after stimulus repetition is affected by an interplay between sensitization and habituation.
Methods: AEPs were recorded in 18 healthy participants. Stimulation consisted of trains with eight tones. The 6th stimulus of each train was a frequency deviant. The N100 amplitude to the 1st stimulus of the train was quantified in each trial. Trials with initially strong N100 responses and with initially weak N100 responses were averaged separately.
Results: For the total trial sample, the N100 and P200 amplitudes decreased from the 1st to the 2nd stimulus of the train but not thereafter. Trials with an initially strong N100 response were qualified by likewise larger N100 amplitudes to the 2nd stimulus, as compared to trials with initially weak N100 responses, and were characterized by a pronounced N100 amplitude decrease from standards to deviants.
Conclusion: Our findings are difficult to reconcile with the view that the response decrement of AEP components after stimulus repetition is modulated by sensitization and habituation, as no evidence for either of these two processes could be obtained.
Significance: The study provides further evidence against habituation as underlying mechanism for the AEP decrement after stimulus repetition.

1. Introduction

Auditory stimulus repetition leads to a decrease of cortical responses, as measured by auditory evoked potentials (AEPs) and auditory evoked fields (AEFs). This response decrease is observed when the to-be-repeated stimulus is preceded by a relatively long time period without stimulation and is repeated within a relatively short time period (Ritter et al., 1968). A typical example for an experimental set-up to investigate this kind of response decrease is the paired-click paradigm. In this paradigm, pairs of clicks are presented that are separated by 8000–12,000 ms, whereas the clicks within the pairs are separated by only 500 ms. Under such conditions the amplitudes of the AEP component P50, but also of the N100 and P200, strongly decrease from the 1st to the 2nd click. Patients with schizophrenia often show a diminished response decrease from the 1st to the 2nd click (for review de Wilde et al., 2007; Patterson et al., 2008).

The predominant interpretation of this finding is that it reflects impaired sensory filtering, leading to its label as *sensory gating*

* Corresponding author at: Department of Psychology, Experimental Neuropsychology Unit, Saarland University, Campus, Building A2.4, 66123 Saarbrücken, Germany. Tel.: +49 681 302 64367.
E-mail address: trosburg@mx.uni-saarland.de (T. Rosburg).

http://dx.doi.org/10.1016/j.clinph.2015.04.071
1388-2457/

deficit. This deficit is, however, not specific for patients with schizophrenia; similar findings were obtained in other neuropsychiatric patients, such as patients with post-traumatic stress disorder (Neylan et al., 1999), patients with bipolar disorder (Lijffijt et al., 2009), or cocaine-dependent subjects (Boutros et al., 2006). Moreover, it is still debated to what extent a diminished response decrease from the 1st to the 2nd click actually reflects impaired sensory filtering: some recent studies reported associations between self-reported perceptual anomalies (Micoulaud-Franchi et al., 2012, 2014), while previous studies failed to reveal such associations (Jin et al., 1998; Johannesen et al., 2008).

Pharmacological challenge studies have been informative about neurotransmitters involved in this kind of response suppression and emphasized the role of nicotinic acetylcholine receptors (Adler et al., 1992, 1993; Turetsky et al., 2012; Knott et al., 2013). Furthermore, studies using electroencephalography (EEG), magnetoencephalography (MEG), electrocorticography (ECoG), and fMRI provided some knowledge about brain structures that form the neural network underlying the processing of such auditory stimuli. This network encompasses not only sensory areas, but also areas in the frontal cortex, thalamus, and hippocampus (Grunwald et al., 2003; Thoma et al., 2003; Rosburg et al., 2004; Boutros et al., 2005, 2008; Korzyukov et al., 2007; Kurthen et al., 2007; Tregellas et al, 2007, 2009; Weiland et al., 2008; Mayer et al., 2009; Ji et al., 2013; Bak et al., 2014). However, these studies need to be considered as descriptive rather than as causal. Bilateral hippocampal sclerosis for example does not lead to a significant disruption of sensory gating (Rosburg et al., 2008).

Although a vast number of studies have been published that investigated sensory gating, it is yet not fully understood what neural or behavioral factors actually lead to the response decrement of AEP components after repeated stimulation. Broadly, there are two fractions of accounts for explaining the decrement: one fraction refers the decrement to habituation as a simple form of learning; the second fraction refers the decrement to characteristics of the involved neural cell assemblies. Within this second fraction, some studies consider the role of inhibitory interneurons as critical (e.g. Freedman et al., 2002; Freedman, 2014), while other studies consider the response decrease more as an intrinsic capacity of the involved (central nervous system) cell-assemblies and conceptualize the response decrease as an effect of refractoriness or stimulus-specific adaptation (e.g. Budd et al., 1998; Ulanovsky et al., 2003; Pérez-González and Malmierca, 2014). Behavioral and neural accounts are not necessarily fully exclusive, since e.g. tonic inhibition descending from higher neural centers has been considered as one cause for habituation (Krasne and Teshiba, 1995).

However, in particular the accounts of habituation and refractoriness predict different response behavior, as initially proposed by Budd et al. (1998). By definition, a process of habituation needs to be qualified by a range of criteria, such as an asymptotic response decrease, stimulus specificity, and dishabituation (Thompson and Spencer, 1966; Rankin et al., 2009). In contrast, refractoriness refers to the recovery time for cell assemblies underlying the AEP response before they are fully responsive again. Consequently, the amplitudes of AEP responses are to a great extent determined by the time intervals between the auditory stimuli, with shorter intervals generally being associated with smaller AEP amplitudes (e.g. Davis et al., 1966; Roth and Kopell, 1969; Rosburg et al., 2010), albeit this might not apply for very short intervals of <500 ms (Budd and Michie, 1994). Furthermore, the reductions of AEP components are greater the more the cell assemblies overlap that generate the AEP responses to two succeeding tone events (e.g. Butler, 1968). For the spectral content of sounds, the latter effect is likely due to the tonotopic organization of the auditory cortex (Saenz and Langers, 2014). The different predictions of habituation and refractoriness on the response behavior are summarized in Table 1. Considering the wide range of clinical populations in which the decremental responses to repeated auditory stimuli have been studied, it is of high relevance to empirically differentiate between the accounts of habituation and refractoriness, with many implications for future research (as e.g. for the design of experiments and studies, as well as for the development of potential intervention programs in clinical populations).

In order to test the predictions of the habituation and refractoriness accounts, trains of identical stimuli that were interspersed with deviant sounds have been used as stimulus material. From our point of view, such studies provided little to no empirical evidence for habituation as underlying mechanism for the response decrease of AEP/AEF components after repeated stimulation: there is a handful of studies on the short-term decrement of AEP/AEF components that showed an asymptotic response decrease (EEG: Ritter et al., 1968; Fruhstorfer et al., 1970; Woods and Elmasian, 1986; MEG: Sörös et al., 2001), another study showed a continuous decrease (EEG: Öhman and Lader, 1972). In contrast, the vast majority of studies revealed that the response decrease was completed with the presentation of the 2nd stimulus of a train (EEG: Roth and Kopell, 1969; 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, 2010; Grau et al., 2007; Fuentemilla et al., 2009; Zhang et al., 2009, 2011; Yadon, 2010; Lucas, 2012; MEG: Lammertmann et al., 2001; Rosburg, 2004; Rosburg et al., 2010; Sörös et al., 2006, 2009; Lagemann et al., 2012; Muenssinger et al., 2013b; Okamoto and Kakigi, 2014). More noteworthy, no study found evidence for dishabituation (Fruhstorfer, 1971; Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2006; Yadon, 2010; Muenssinger et al., 2013b). As predicted by the refractoriness account, response recovery was present for large frequency deviants (Woods and Elmasian, 1986; Barry et al., 1992; Yadon, 2010), but absent for duration deviants (Rosburg et al., 2006). Furthermore, as also predicted by the refractoriness account, repeated stimulation at long interstimulus intervals did not result in AEP response decrements (Ritter et al., 1968; Budd et al., 1998; MacDonald and Barry, 2014).

Nevertheless, some recent studies from a MEG research group in Tuebingen (Germany) have argued in favor of habituation as the underlying mechanism for the response decrease of AEP/AEF components after repeated stimulation (Matuz et al., 2012; Muenssinger et al., 2013a,b). In a study on fetuses and neonates, Muenssinger et al. (2013a) have argued with reference to the dual-process theory of response habituation (Groves and Thompson, 1970) that an initial response increase (from the 1st to the 2nd tone of a stimulus train) and subsequent response

Table 1
Habituation vs. refractoriness: predicted response behavior for repeated auditory stimulation.

	Habituation	Refractoriness
Stimulus repetition	Asymptotic response decrease	Response decrease completed after the 2nd stimulus; decrease is absent at long interstimulus intervals
Presentation of deviants	Response recovery	Response recovery possible, in particular when the tone pitch of the deviant strongly varies from the standard tone
Presentation of repeated sounds after the deviant	Dishabituation (response recovery to the previously "habituated" stimulus)	Response recovery at best small; absent when the tone pitch of the deviant is similar to the standard tone

decrease (from the 2nd to the 3rd tone) can be regarded as evidence for habituation. Indeed, Groves and Thompson (1970) have described that animals might first show an increase in responsiveness to repeated stimulation (sensitization) and later a decrease in responsiveness (habituation). However, AEP/AEF studies in human adults that presented trains of identical auditory stimuli always showed an initial response decrease (e.g. Ritter et al., 1968; Fruhstorfer et al., 1970; Barry et al., 1992; Budd et al., 1998; Rosburg, 2004; Rosburg et al., 2004, 2006, 2010; Sörös et al., 2006, 2009; Zhang et al., 2009, 2011). Thus, as we have also noted in a recent commentary (Rosburg, Weigl, & Sörös, 2014), the observed response pattern of Muenssinger et al. (2013a) is at odds with adult data.

Yet, taking the argumentation of Muenssinger et al. (2013a) into account, we have to acknowledge that an interplay between habituation and sensitization might represent an aspect that has not been appropriately addressed in previous AEP/AEF studies. In a recent theoretical approach, the behavioral homeostasis theory (BHT), Eisenstein et al. (2012) have argued that the level of alertness prior to stimulation is critical whether an organism shows a response decrease (habituation) or increase (sensitization) to iterative stimuli. According to the BHT, strong initial responses are followed by weak ones (habituation) and small behavioral responses by stronger ones (sensitization). Following this line of argumentation, habituation might occur in some trials and sensitization in others. Consequently, averaging across all trials might lead to wrong conclusions. In the current study, we tested the predictions of the BHT by selectively averaging trials with initially large and with initially weak responses.

For this purpose, AEPs were recorded in a sample of healthy participants. Stimulation consisted of trains of eight tones (S1 to S8), with a frequency deviant at the 6th position. First, the effects of tone repetition were analyzed for the AEP data averaged across all trials in order to replicate previous findings that provided counterevidence for habituation as the underlying factor for the decrement of AEP/AEF components after repeated simulation. This counterevidence included in particular the lack of an asymptotic response decrease and the lack of dishabituation after presenting a deviant stimulus (Table 1; Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2004, 2006, 2010).

Second, we conducted a single-trial based analysis of the AEPs. The amplitudes of the N100 were quantified in each trial. Trials that showed a large N100 to the initial stimulus of the train (above individual median) and trials that showed small N100 to the initial stimulus of the train (below individual median) were averaged separately. The same trials were also averaged for the subsequent stimuli in the train. The BHT suggests that habituation and sensitization are active processes and that their occurrence depends on the strength of the initial response (Eisenstein et al., 2012). We tested whether AEP responses to subsequent stimuli were indeed *larger* when the initial response was small than when the initial response was large. In contrast, the AEP responses to these stimuli should not vary in dependence on the initial response if regression to the mean is the only rule that applies (Stigler, 1997; Eisenstein et al., 2012). For trial classification, we focused on the N100 amplitude because previous studies have indicated that increased N100 amplitudes are associated with increased levels of alertness and attention (Hillyard et al., 1973; Näätänen et al., 1981; Näätänen and Picton, 1987; Crowley and Colrain, 2004).

Third, according to the BHT, the level of alertness prior to stimulation is supposed to be critical whether an organism shows a weak or strong response to the initial stimulus. It has been proposed that the levels of alertness are reflected in the levels of theta (4–8 Hz) and alpha band power (8.5–12 Hz) (Klimesch et al., 1996, 2007; Klimesch, 1999; Barry et al., 2011). Consequently, theta and alpha band activity in the pre-stimulus interval should show some co-variation with the magnitude of the initial AEP response. Already more previously, in a systems-theoretical account, it has been suggested that the magnitude of evoked responses can be predicted from the spontaneous activity preceding the stimulation (Başar et al., 1979). This relation between the prestimulus EEG activity and subsequent N100 has been investigated in number of studies, but revealed some conflicting results (Başar and Stampfer, 1985; Romani et al., 1988; Jansen and Brandt, 1991; Brandt et al., 1991; Haig and Gordon, 1998; Barry et al., 2000, 2011; de Blasio and Barry, 2013a,b; de Blasio et al. 2013; for conceptual overview see Barry et al., 2003). The findings of Başar and Stampfer (1985) and Rahn and Başar (1993) support the prediction of the BHT that decreased levels of alertness (high levels of alpha activity) at the time point of stimulation are followed by smaller N100 responses, whereas the studies of Jansen and Brandt (1991) and Barry et al. (2000) reported an opposite pattern (with high levels of alpha activity being followed by larger N100 responses). In the current study, we sought to clarify this issue and tested whether large levels of theta and low levels of alpha pre-stimulus activity were followed by large AEP responses to the 1st stimulus, as it can be presumed on the basis of the BHT.

2. Methods

2.1. Participants

18 volunteers (10 female), ranging in age from 19 to 35 years (mean age 25 years) took part in the experiment. All participants were students at Saarland University, reported to have no psychiatric or neurological history, as well as no hearing deficit. One additional participant with a hearing deficit was excluded, as well as two other participants whose recordings were prematurely terminated due to technical failures. All participants were informed about the procedure of the experiment and gave written consent for participation. Participation was compensated with 8 €/h.

2.2. Stimulation

Auditory stimuli were presented by two loudspeakers placed about 1 m to the left and to the right in 45° angles in front of the participants. Stimulation consisted of 100 trains of 8 sine tones each. Trains were separated by a randomized interval between 6000 and 7000 ms. Tones within the train were separated by a stimulus onset asynchrony (SOA) of 1026 ms. All tones had 50 ms sound duration (including 5 ms rise and fall time) and were presented at 70 dB sound pressure level. Seven stimuli were 800 Hz tones; one was an 850 Hz tone. The 850 Hz tone (deviant) was always presented at the 6th position of the train. The commercial software EPrime 2.0 (Psychology Software Tools, Sharpsburg, PA, USA) was used for stimulation. During stimulation, the participants watched a nature film with the tone switched off (“One Life”, BBC Earth), with no further task required; tone stimuli did not require any behavioral response either. All participants were tested at the end of an unrelated (effortful) memory experiment. The recording time for the tone experiment was about 25 min. At the beginning of the tone experiment, participants rated their momentary sleepiness on a seven-point Likert scale ranging from −3 (very alert) to very sleepy (+3).

2.3. EEG recording

EEG was recorded with 58 embedded silver/silver chloride EEG electrodes that were attached to the participant’s head in an elastic cap (Easycap, Herrsching, Germany). Electrode locations in the used caps are based on an extended 10–20 system (Fp1, Fpz, Fp2,

AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2). Furthermore, electrodes were placed manually at the two mastoids (A1, A2). Electrode impedances were kept below 5 kΩ. EEG was continuously recorded, referenced to the left mastoid. In addition, electroocular activity was recorded by a pair of electrodes affixed to the outer canthi and by a pair of electrodes placed below and above the right eye. Data were sampled at 500 Hz and filtered online from 0.016 Hz (time constant 10 s) to 250 Hz.

2.4. Data analysis

EEG data were analyzed with BrainVision Analyzer 2.04 (Brain Products, Gilching, Germany). Offline, data were digitally filtered from 0.1 Hz to 40 Hz (48 dB), with an additional notch filter at 50 Hz to suppress line activity, and re-referenced to linked mastoids. Data were segmented into epochs of 8500 ms duration starting 500 ms before the onset of the initial stimulus of the train (S1). The influence of eye movements and blinks on EEG activity, as well as of electrocardiographic and other artifacts was corrected by an independent component analysis (ICA). Subsequently, epochs were screened for further artifacts. On average 5 segments (range 0–19) with voltage steps larger than 50 μV/ms or with amplitudes exceeding ±70 μV were rejected as artifacts. After artifact rejection, data were segmented in shorter epochs of 1000 ms duration with 200 ms as a pre-stimulus baseline, for each stimulus in the train (S1 to S8) separately.

Analysis across all trials: In a first set of analyses, we tested whether the AEP data showed a response decrease from S1 to S2, a response recovery from S5 to S6 (deviant), an asymptotic decrease, and dishabituation in order to replicate previous findings. We used 9 electrodes over frontal (F1/Fz/F2), frontocentral (FC1/FCz/FC2), and central (C1/Cz/C2), regions for these analyses of repetition effects on conventionally averaged AEPs (i.e. averaged across all trials without artifacts). In order to test whether AEPs showed a significant response decrement from S1 to S2, the average N100 and P200 amplitudes were subjected to repeated measure analysis of variance (ANOVA) with TONE (S1 vs. S2), ANTERIORITY (F, FC, C electrodes), and LATERALITY (1, *z*, 2 electrodes) as within-subjects factors. The N100 and P200 amplitudes were quantified as the mean amplitude in 28-ms time windows around the grand average peak maximums, corresponding to 7 sampling points before and after the peaks, relative to the baseline of 200 ms. Different latency windows were chosen for quantifying the N100 and P200 amplitudes to S1 and S2, since there was a substantial peak latency decrease after S1. The time windows were 94–122 ms and 190–218 ms for the N100 and P200 to S1, and 84–112 ms and 154–182 ms for the N100 and P200 to S2, respectively. The criteria for habituation were tested in three further repeated measure ANOVAs with TONE, ANTERIORITY, and LATERALITY as within-subjects factor that specifically contrasted the N100 and P200 amplitudes to two other stimuli of the train each (i.e. the factor TONE varied between these analyses): An asymptotic decrease was presumed to be reflected in larger AEP responses to S2 than to S8; response recovery was presumed to be reflected in larger N100 responses to the deviant stimulus (S6) than to the preceding repeated stimulus (S5); dishabituation was presumed to be reflected in larger AEP responses to S7 than to the preceding repeated stimulus (S5). Paired *t*-tests were used for post-hoc testing. The N100 and P200 amplitudes to S5, S6, S7, and S8 were quantified in the same 28-ms time window as used for the analysis of the AEPs to S2.

Trial selective averaging: For analyzing the effects of the initial response on the later responses in the very same trial, the *n* trials of each participant were separated by median-split in trials with large N100 responses to S1 and small N100 responses to S1 ('High $N1_{S1}$' vs. 'Low $N1_{S1}$' trials). For this, the N100 amplitudes in each trial were exported to SPSS (IBM, USA) and quantified at the individual S1 peak latency of the average response in a 28-ms time window at electrode FCz. Thus, the selected time windows varied between subjects, but not between trials within a subject. The identified N100 peaks were manually confirmed. In case of odd trial numbers, the median trial was excluded when creating the two subsamples. Subsequently, the AEPs to the subsequent stimuli (S2 to S8) were averaged across 'High $N1_{S1}$' vs. 'Low $N1_{S1}$' trials. According to the BHT, the AEP amplitudes to S2 should be larger for trials that showed an initially weak N100 response ('Low $N1_{S1}$' trials) than for trials that an initially strong N100 response ('High $N1_{S1}$' trials). Moreover, according to the BHT, habituation and sensitization are presumed to maximize the organism's overall readiness to cope with new stimuli. Thus, the AEPs to deviants (S6) and standards following the deviant (S7) should not differ between the two kinds of trials. These predictions were tested in repeated measure ANOVAs with TRIAL TYPE ('High $N1_{S1}$' vs. 'Low $N1_{S1}$'), ANTERIORITY (*F*, FC, *C* electrodes), and LATERALITY (1, *z*, 2 electrodes) as within-subjects factors. As dependent variables, we entered the N100 and P200 amplitudes of each AEP (at the same latency windows as used above), as well as the amplitude of the mismatch negativity (MMN). The MMN represents a specific response to sound deviance in an otherwise regular sound stimulation (for review Näätänen et al., 2001). The MMN was extracted from the difference potential between the AEP to S6 (deviants) and the AEP to S2 to S4 (standards) as the mean amplitude between 150 and 230 ms, again for 'Low $N1_{S1}$' and 'High $N1_{S1}$' trials separately.

For the analysis of the theta and alpha activity, only responses to S1 were considered. Two segments were extracted from each 8500 ms epoch: one from −500 to 0 ms (S1 pre-stimulus activity) and another from 0 to 500 ms (S1 post-stimulus activity). A Fast Fourier Transformation (FFT) was run with 0.5 Hz frequency resolution, using a rectangular window, a padratio of 4.096, and no normalization. FFT data of each trial were exported. Mean theta (4–8 Hz) and alpha (8.5–12 Hz) amplitude values were calculated and compared between the two subsamples of trials in a repeated measure ANOVA with TRIAL TYPE ('High $N1_{S1}$' vs. 'Low $N1_{S1}$'), ANTERIORITY (*F*, FC, *C* electrodes), and LATERALITY (1, *z*, 2 electrodes) as within-subjects factors. To further elucidate the relation between oscillatory activity and the N100 amplitude within trials, Pearson product-moment correlations between individually *z*-transformed theta and alpha pre- and post-stimulus activity and the individually *z*-transformed N100 and P200 amplitudes to S1 in each trial were calculated.

3. Results

Sleepiness ratings were obtained in 17 of the 18 participants. Average rating was −0.1 (range −3 to +2), with 13 of the participants giving ratings between −1 and +1. To sum it up, at the time point of testing, participants were neither particularly alert nor particularly sleepy.

3.1. Effects of stimulus repetition across trials

The repetition effects across trials are depicted in Fig. 1A for the AEPs at FCz; the mean amplitude values (±SD) at this electrode can be found in Table 2. The results of the *F* statistics are found in Table 3. The N100 and P200 amplitudes showed a strong decrease from S1 to S2. Post-hoc tests showed that the N100 and P200 amplitudes to S1 were larger than the N100 and P200 amplitudes to S2 at all analyzed electrodes (all $ts_{17} > 4.000$, $p < 0.001$). The

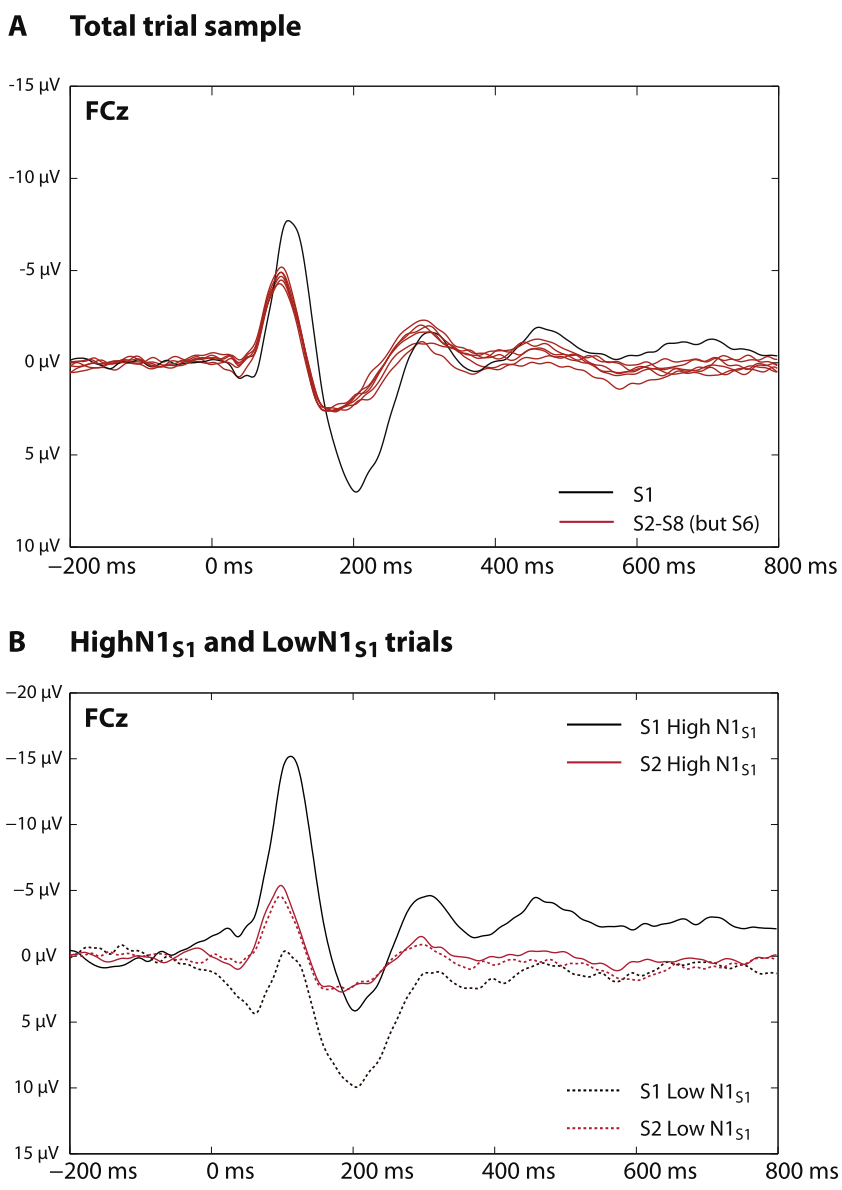

Fig. 1. (A) Grand average AEP for the total trial sample at electrode FCz: the AEP in response to the 1st stimulus (S1) of a train is shown as black line; the AEPs to the subsequent stimuli (but the deviant) as red lines. The amplitudes of the AEP components N100 and P200 to S1 clearly surmounted the N100 and P200 amplitudes to the subsequent stimuli, with no systematic variation between the latter. (B) AEPs to S1 and S2 for trials with an initially large N100 response ('High $N1_{S1}$', continuous lines) and for trials with an initially small N100 response ('Low $N1_{S1}$', dashed lines). The responses to S1 are shown as black lines, the responses to the 2nd stimulus (S2) as red lines.

Table 2
Mean N100 and P200 amplitudes.

FCz		S1	S2	S3	S4	S5	S6	S7	S8
N100	All	−7.2 (2.7)	−4.4 (2.3)	−4.3 (2.7)	−4.8 (2.2)	−4.5 (2.3)	−3.8 (2.3)	−4.0 (2.1)	−4.1 (2.2)
	$N1_{S1}$ low	0.0 (2.7)	−4.1 (2.8)	−3.8 (2.7)	−4.6 (2.7)	−4.4 (2.3)	−4.1 (2.3)	−3.8 (1.9)	−4.1 (2.2)
	$N1_{S1}$ high	−14.5 (3.2)	−4.9 (2.2)	−4.8 (3.0)	−5.0 (2.3)	−4.6 (2.7)	−3.5 (2.6)	−4.2 (2.5)	−4.1 (2.3)
P200	All	6.7 (4.1)	2.4 (2.4)	2.5 (2.6)	2.4 (2.4)	2.6 (2.4)	–	2.5 (2.9)	2.7 (1.9)
	$N1_{S1}$ low	9.7 (3.8)	2.4 (2.4)	2.9 (2.9)	2.5 (2.8)	2.5 (2.3)	–	2.4 (3.1)	2.6 (2.5)
	$N1_{S1}$ high	3.8 (4.7)	2.4 (2.8)	2.2 (2.7)	2.3 (2.6)	2.7 (3.1)	–	2.8 (3.1)	2.8 (1.9)

Mean N100 and P200 amplitude values in µV (±standard deviations) in response to the eight stimuli of the train, for the total sample and for the separate trial samples (high vs. low N100 amplitudes to S1). S6 as a sound deviant elicited a mismatch negativity (MMN) that overlapped with the P200. Consequently, the P200 amplitude could not be quantified unambiguously in this AEP.

presentation of deviants did not result in a N100 response recovery. Instead, the N100 amplitudes slightly decreased from S5 to S6. This decrease was significant at the frontal and fronto-central electrodes (all $ts_{17} > 2.209$, $p < 0.05$) but not at central electrodes (all $ts_{17} < 1.782$, n.s.). As expected, deviants elicited a MMN that was significant at all nine analyzed electrodes (one-sample *t*-tests: all $ts_{17} > 4.673$, ps < 0.001). Due to the spatio-temporal overlap of P200 and MMN activity, the presence of a P200 response recovery

Table 3
Response decrease after stimulus repetition across all trials.

	TONE	TONE x ANTERIORITY	TONE x LATERALITY	TONE x ANTERIORITY x LATERALITY
Response decrease (S1 vs. S2)				
N100	$F_{1,17} = 24.878$ $p < 0.001$ $\eta^2 = 0.594$	$F_{2,34} = 0.852$ n.s. $\eta^2 = 0.048$	$F_{2,34} = 8.071$ $p = 0.001$ $\eta^2 = 0.322$	$F_{4,68} = 2.214$ $p = 0.015$ $\eta^2 = 0.192$ $\varepsilon = 0.671$
P200	$F_{1,17} = 49.718$ $p < 0.001$ $\eta^2 = 0.745$	$F_{2,34} = 17.313$ $p < 0.001$ $\eta^2 = 0.505$ $\varepsilon = 0.563$	$F_{2,34} = 7.247$ $p = 0.002$ $\eta^2 = 0.299$	$F_{4,68} = 6.125$ $p = 0.002$ $\eta^2 = 0.265$ $\varepsilon = 0.669$
Asymptotic decrease (S2 vs. S8)				
N100	$F_{1,17} = 1.328$ n.s. $\eta^2 = 0.072$	$F_{2,34} = 0.006$ n.s. $\eta^2 < 0.001$	$F_{2,34} = 0.252$ n.s. $\eta^2 = 0.015$	$F_{4,68} = 2.193.$ n.s $\eta^2 = 0.114$ $\varepsilon = 0.671$
P200	$F_{1,17} = 0.505$ n.s. $\eta^2 = 0.029$	$F_{2,34} = 0.096$ n.s. $\eta^2 = 0.006$	$F_{2,34} = 0.503$ n.s. $\eta^2 = 0.029$	$F_{4,68} = 0.730$ n.s. $\eta^2 = 0.041$
Response recovery (S5 vs. S6)				
N100	$F_{1,17} = 5.005$ $p = 0.039$ $\eta^2 = 0.227$	$F_{2,34} = 1.913$ n.s. $\eta^2 = 0.101$	$F_{2,34} = 0.460$ n.s. $\eta^2 = 0.026$	$F_{4,68} = 4.497$ $p = 0.003$ $\eta^2 = 0.209$
P200	Not tested (MMN overlap)			
Dishabituation (S5 vs. S7)				
N100	$F_{1,17} = 2.615$ n.s. $\eta^2 = 0.133$	$F_{2,34} = 1.176$ n.s. $\eta^2 = 0.065$	$F_{2,34} = 0.141$ n.s. $\eta^2 = 0.008$	$F_{4,68} = 0.867$ n.s. $\eta^2 = 0.049$
P200	$F_{1,17} = 0.055$ n.s. $\eta^2 = 0.003$	$F_{2,34} = 0.250$ n.s. $\eta^2 = 0.015$	$F_{2,34} = 1.245$ n.s. $\eta^2 = 0.068$	$F_{4,68} = 3.370$ $p = 0.030$ $\eta^2 = 0.165$ $\varepsilon = 0.682$

The results of the repeated measures ANOVAs across all trials: the factor TONE encompassed different contrasts in each ANOVA. Significant main effects of TONE are marked by black edging. Please note that the significant main effect of TONE for response recovery indicates a significant response decrease from S5 to S6 (and not an increase).

from S5 to S6 could not be analyzed. The further ANOVAs revealed neither evidence for an asymptotic decrease of N100 and P200 amplitudes (S2 vs. S8 contrast) nor for a response recovery in the response to the standard following the deviant (S5 vs. S7 contrast, Table 3).

Taken together, both the N100 and P200 amplitudes showed a strong initial decline from S1 to S2, but there was no indication for a further, asymptotic decrease, no indication that the presentation of the deviant tone resulted in a response recovery, and no indication of dishabituation.

3.2. Consequences of strong responses to S1 (trial selective averaging)

The BHT suggests that the initial level of activation determines the subsequent magnitude of the response. Trials with an initially large N100 were compared with trials with an initially weak N100 by median split of the total trial sample. The mean amplitude values (±SD) at FCz for the two-subsamples can be found in Table 2; the results of the *F* statistics are found in Table 4. For the S2 responses, the comparison of the two-subsamples revealed a marginally significant influence of TRIAL TYPE: The N100 amplitudes to S2 tended to be larger in trials with an initially large N100 than in trials with an initially weak N100, whereas the P200 amplitudes to S2 did not show any variation between the two kinds of trials (Fig. 1B). A similar pattern of results was observed for the AEPs to standard tones (S2 to S4): The N100 amplitudes to standards were significantly larger in trials with an initially large N100 than in trials with an initially weak N100, whereas the P200 amplitudes again did not differ.

For the S6 responses, we found an opposite pattern: We observed a trend for smaller N100 amplitudes in 'High $N1_{S1}$' trials, as compared to 'Low $N1_{S1}$' trials (Table 4). Pairwise comparisons at individual electrodes showed trends for smaller N100 amplitudes at FC1, FCz, FC2, and *F*2 (1.748 < all ts < 1.950, all ps < 0.1). Thus, the N100 amplitudes to S6 (as *unrepeated* stimulus) paradoxically showed (on a trend level) a response behavior that was predicted on the basis of the BHT for repeated stimuli.

In order to elucidate the differential trial type effects on stimulus processing in more detail, a repeated measure ANOVA with STIMULUS ('standards' vs. 'deviants'), TRIAL TYPE ('High $N1_{S1}$' vs. 'Low $N1_{S1}$'), ANTERIORITY (*F*, FC, *C* electrodes), and LATERALITY (1, *z*, 2 electrodes) was run. This analysis revealed a differential effect of trial type on the N100 amplitudes to standards (S2 to S4) and deviants (S6) in 'High $N1_{S1}$' trials, but not in 'Low $N1_{S1}$' trials (TRIAL TYPE × STIMULUS interaction: $F_{1,17} = 14.735$, $p = 0.001$, $\eta^2 = 0.464$): In 'High $N1_{S1}$' trials, the N100 amplitude to standards was larger than the N100 amplitudes to deviants ($F_{1,17} = 13.624$, $p = 0.002$, $\eta^2 = 0.445$), whereas no such difference was observed in 'Low $N1_{S1}$' trials ($F_{1,17} = 0.009$, n.s., $\eta^2 = 0.001$) (Fig. 2 A and B). This also led to a positive N100 deflection in the difference potential in 'High $N1_{S1}$' trials, but not in 'Low $N1_{S1}$' trials (Fig. 3). The MMN amplitudes themselves were significantly *larger* in 'Low $N1_{S1}$' trials than in 'High $N1_{S1}$' trials (Table 4). Pairwise comparisons at individual electrodes showed that the MMN differences between the two kinds of trials were somewhat larger at frontal electrodes (2.548 < all ts < 3.212, 0.005 < ps < 0.021) than at central electrodes (1.972 < all ts < 2.077, 0.053 < ps < 0.066).

For the AEPs to S7 (standard following the deviant), the analysis revealed neither for the N100 nor the P200 significant amplitude differences between the two kinds of trials. Taken together, 'High $N1_{S1}$' trials were qualified by larger N100 amplitudes to subsequent repeated stimuli, as compared to 'Low $N1_{S1}$' trials. In contrast, the N100 amplitudes to deviants, as well as the MMN amplitudes were reduced in trials with an initially large N100, as compared to 'Low $N1_{S1}$' trials.

3.3. S1 pre- and post-stimulus oscillatory activity

The BHT suggests that the initial response reflects the individual's activation in this specific trial. Accordingly, the pre-stimulus theta and alpha activity were presumed to vary with the N100 response to S1. This prediction could not be verified: The pre-stimulus theta and alpha activity (−500 ms to 0 ms) did not differ between trials with high and low N100 responses to S1 (main effects TRIAL TYPE theta: $F_{1,17} = 0.001$, n.s.; alpha: $F_{1,17} = 0.646$, n.s., Fig. 4, Table 5). Interactions between TRIAL TYPE and the two electrode location factors (ANTERIORITY and LATERALITY) did not reach significance either (theta: $Fs_{2,34} < 1.658$, n.s.; alpha: $Fs_{2,34} < 0.183$, n.s.).

In addition to pre-stimulus activity, post-stimulus theta and alpha activities were analyzed as well. This analysis was run in order to inform about the validity of the trial-based quantification of the N100 amplitude. This analysis showed significant differences between 'High $N1_{S1}$' and 'Low $N1_{S1}$' trials, with larger theta and alpha activity for larger N100 responses to S1 (main effects TRIAL TYPE theta: $F_{1,17} = 39.900$, $p < 0.001$, $\eta^2 = 0.702$; alpha: $F_{1,17} = 6.042$, $p = 0.025$, $\eta^2 = 0.262$, Table 5). In line with this observation, the *z*-transformed post-stimulus theta and alpha at FCz co-varied with the *z*-transformed N100 and P200 amplitudes to S1 across *all* trials at the same electrode, whereas the *z*-transformed pre-stimulus theta and alpha did not show such correlations (Supplementary Table S1).

Table 4
Contrast between high $N1_{S1}$ and low $N1_{S1}$ subsamples.

	TRIAL TYPE	TRIAL TYPE x ANTERIORITY	TRIAL TYPE x LATERALITY	TRIAL TYPE x ANTERIORITY x LATERALITY
First repeated standard (S2)				
N100	$F_{1,17} = 3.305$ $p = 0.087$ $\eta^2 = 0.163$	$F_{2,34} = 0.341$ n.s. $\eta^2 = 0.020$	$F_{2,34} = 0.733$ n.s. $\eta^2 = 0.041$	$F_{4,68} = 0.290$ n.s. $\eta^2 = 0.017$
P200	$F_{1,17} = 0.055$ n.s. $\eta^2 = 0.003$	$F_{2,34} = 0.182$ n.s. $\eta^2 = 0.011$	$F_{2,34} = 0.300$ n.s. $\eta^2 = 0.017$	$F_{4,68} = 1.395$ n.s. $\eta^2 = 0.076$
Standards (S2 to S4)				
N100	$F_{1,17} = 5.222$ $p = 0.035$ $\eta^2 = 0.235$	$F_{2,34} = 1.134$ n.s. $\eta^2 = 0.063$	$F_{2,34} = 1.112$ n.s. $\eta^2 = 0.061$	$F_{4,68} = 0.340$ n.s. $\eta^2 = 0.020$
P200	$F_{1,17} = 0.505$ n.s. $\eta^2 = 0.029$	$F_{2,34} = 0.096$ n.s. $\eta^2 = 0.006$	$F_{2,34} = 0.503$ n.s. $\eta^2 = 0.029$	$F_{4,68} = 0.730$ n.s. $\eta^2 = 0.041$
Deviants (S6)				
N100	$F_{1,17} = 2.995$ $p = 0.102$ $\eta^2 = 0.150$	$F_{2,34} = 0.615$ n.s. $\eta^2 = 0.035$	$F_{2,34} = 0.050$ n.s. $\eta^2 = 0.003$	$F_{4,68} = 2.593$ $p = 0.071$ $\eta^2 = 0.132$ $\varepsilon = 0.665$
MMN	$F_{1,7} = 6.072$ $p = 0.025$ $\eta^2 = 0.263$	$F_{2,34} = 3.558$ $p = 0.069$ $\eta^2 = 0.173$ $\varepsilon = 0.581$	$F_{2,34} = 0.399$ n.s. $\eta^2 = 0.023$	$F_{4,68} = 0.438$ n.s. $\eta^2 = 0.025$
Standard after the deviants (S7)				
N100	$F_{1,17} = 1.541$ n.s. $\eta^2 = 0.083$	$F_{2,34} = 0.224$ n.s. $\eta^2 = 0.013$	$F_{2,34} = 0.376$ n.s. $\eta^2 = 0.022$	$F_{4,68} = 2.725$ $p = 0.036$ $\eta^2 = 0.138$
P200	$F_{1,17} = 0.441$ n.s. $\eta^2 = 0.025$	$F_{2,34} = 0.040$ n.s. $\eta^2 = 0.002$	$F_{2,34} = 0.266$ n.s. $\eta^2 = 0.015$	$F_{4,68} = 1.992$ n.s. $\eta^2 = 0.105$

The results of the repeated measures ANOVAs of the trial-selective averaging: significant main effects of TRIAL TYPE ('High $N1_{S1}$' vs. 'Low $N1_{S1}$' trials) are marked by black edging, effects on trend level are marked by edging in broken lines.

4. Discussion

4.1. Effects of stimulus repetition in the total trial sample

The effects of tone repetition were analyzed for the data averaged across all trials in order to compare the current results with previous findings. Overall, the observed response pattern was very well in line with the majority of previous studies in adults (e.g. Ritter et al., 1968; Barry et al., 1992; Budd et al., 1998; Rosburg, 2004; Rosburg et al., 2004, 2006, 2010; Zhang et al., 2009, 2011; Sörös et al., 2006, 2009): We observed steep decreases of the N100 and P200 amplitudes from the 1st to the 2nd stimulus of the train but no further decreases thereafter. Moreover, there was no indication for dishabituation: The N100 and P200 amplitudes to the stimulus following the deviant did not show any increase, as compared to the responses to other stimuli in the train. Such a lack of AEP dishabituation has previously been reported by Barry et al. (1992), Budd et al. (1998), Rosburg et al. (2006), and even by Muenssinger et al. (2013b). Finally, deviants elicited a MMN and their presentation was associated with a small decrease of the N100 amplitudes from S5 to S6 rather than with an increase. The elicitation of a MMN indicates that the participants registered the change in the acoustic stimulation. Consequently, the absence of a N100 response recovery by the deviant cannot be explained by the fact that the change was simply not perceived. In conventional passive oddball paradigms with continuous stimulation, small frequency deviants usually are not associated with an N100 increase either (Sams et al., 1985; Pakarinen et al., 2007). In contrast, strong pitch deviants lead to some response recovery of the N100 amplitude (Woods and Elmasian, 1986; Barry et al., 1992; Yadon, 2010). These findings suggest that it is not the change itself that promotes a N100 recovery but the magnitude of pitch change, which supports the view that the response decrease and recovery of the N100 are related to the refractoriness of involved neural generators (Butler, 1968; Budd et al., 1998) or to stimulus specific adaptation (Ulanovsky et al., 2003; Pérez-González and Malmierca, 2014). As we will outline further below, we refer the N100 decrease to deviants to attentional and not physiological factors.

Taken together, the current findings can be considered as further evidence against habituation as the underlying mechanism for the short-term decrement of AEP components after stimulation repetition since three major criteria for habituation (Thompson and Spencer, 1966; Rankin et al., 2009) were not met: The response decrease was not asymptotic, there was no indication of a response recovery when a deviant was presented, and the presentation of a deviant was not followed by dishabituation.

4.2. The impact of the initial N100 response on the processing of subsequent stimuli

The BHT suggests that habituation and sensitization are active processes and that their occurrence depends on the strength of the initial response (Eisenstein et al., 2012). The current study tested whether AEP responses to subsequent stimuli were larger when the initial N100 response was small than when the initial N100 response was large, as predicted by the BHT. However, our analysis revealed marginally larger N100 amplitudes in 'High $N1_{S1}$' trials, as compared to 'Low $N1_{S1}$' trials, and no difference in the P200 amplitudes. Thus, our analysis provided no evidence that the AEP response decrease is modulated by an interplay between habituation and sensitization, as formulated by the BHT. Instead, the observed pattern for the S2 responses might, at first glance, be considered as support for Sokolov's neuronal model of the orienting reflex (OR) (Sokolov, 1963). According to Sokolov's model, phasic ORs are amplified by the current arousal state and large initial responses are followed by stronger S2 responses (see also Barry, 2004; Steiner and Barry, 2011). However, we also observed a significant decrease of the N100 amplitudes from standards (S2 to S4) to deviants (S6) in 'High $N1_{S1}$' trials, whereas these N100 amplitudes did not vary in 'Low $N1_{S1}$' trials, and this finding is contrary to predictions of the BHT and Sokolov's model: According to the BHT, habituation and sensitization are presumed to maximize the organism's overall readiness to cope with new stimuli. Thus, the BHT would predict similarly strong responses to deviants in 'High $N1_{S1}$' and 'Low$N1_{S1}$' trials. According to Sokolov's model, stronger arousal states should be associated with larger responses to both standards and deviants, whereas we found a decrease of the N100 amplitude from standards to deviants in 'High $N1_{S1}$' trials.

What other factor could explain this finding? Selective attention is known to affect the N100 amplitude (Hillyard et al., 1973; Näätänen et al., 1981). As a tentative explanation, we consider that in 'High $N1_{S1}$' trials participants might have directed more attention towards standard stimuli than to deviant stimuli, leading to the observed differential processing of standards and deviants in such trials. Thus, we argue that the magnitude of the N100 amplitude to S1 might, aside from other factors, reflect a differential allocation of selective attention. However, we acknowledge that this explanation remains speculative as selective attention was neither required nor controlled in the current study. In addition to the N100, the MMN amplitudes varied between 'High $N1_{S1}$' and 'Low $N1_{S1}$' trials, as well: The amplitudes were on average smaller in 'High $N1_{S1}$' than in 'Low $N1_{S1}$' trials. We consider this effect as secondary to the observed N100 modulation: In 'High $N1_{S1}$' trials, the larger N100 amplitudes to standards than to deviants resulted in a positive deflection in the difference potential and this positivity

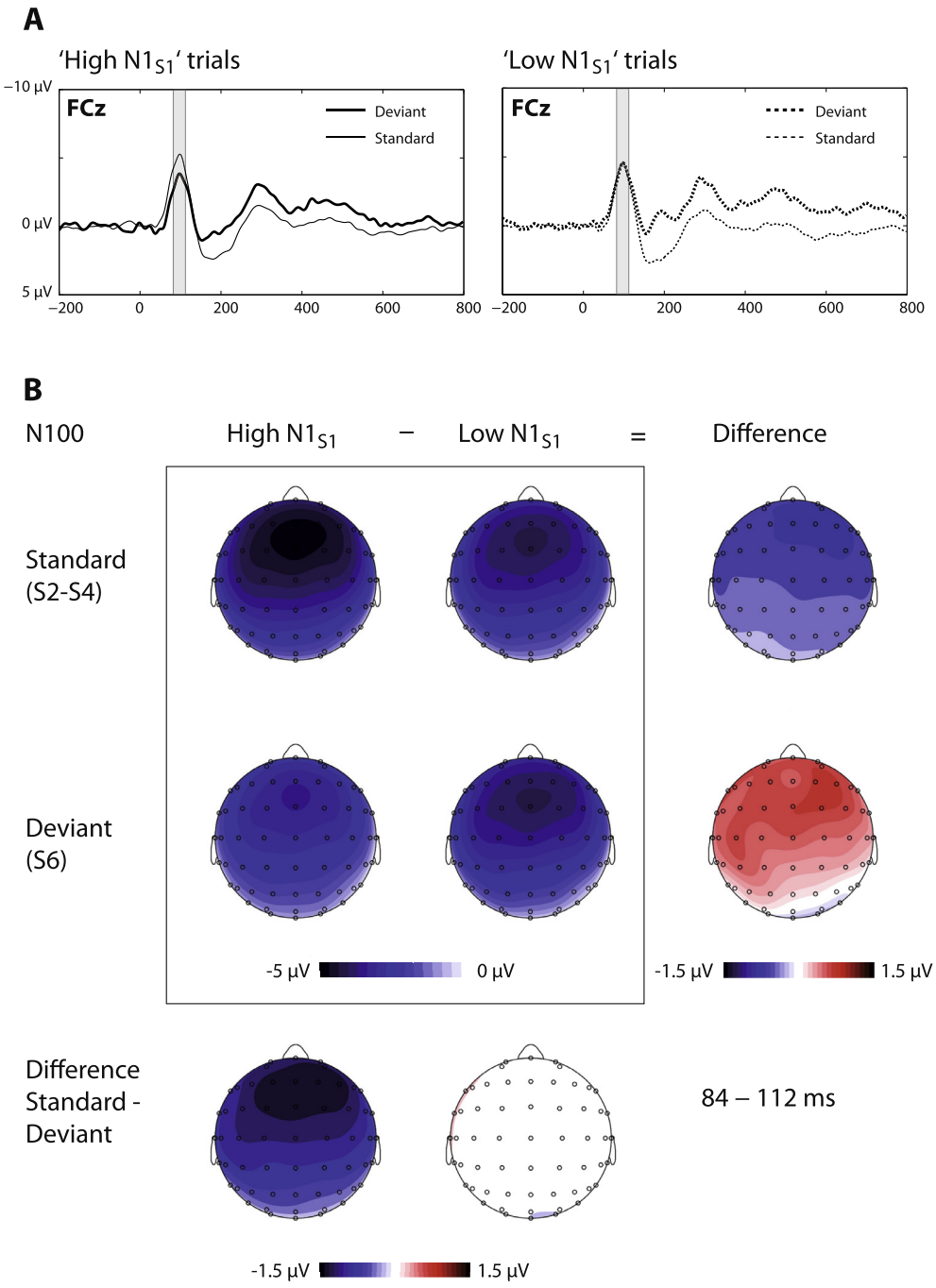

Fig. 2. (A) AEPs to standards (S2 to 4) and deviants (S6) for 'High $N1_{S1}$' trials (continuous lines) and 'Low $N1_{S1}$' trials (dashed lines). The N100 latency range (84–112 ms) is marked by gray shading. (B) The N100 to standards and deviants in their scalp distribution, for the two kinds of trials separately ('High $N1_{S1}$' trial data in the left column, 'Low $N1_{S1}$' data in middle column, and the difference between the two in right column); the difference between standards and deviants is depicted in the bottom row; only for 'High $N1_{S1}$' trials, a significant decrease of the N100 amplitude from standards (S2 to S4) to the deviants (S6) was observed.

might have diminished the subsequent MMN by component overlap (Fig. 3).

It is important to note that the current findings should not and cannot be regarded as counterevidence for the BHT in general, also because the BHT does not define the range of biological responses for which it is assumed to be valid (Eisenstein et al., 2006, 2012). However, recent studies on the skin conductance response (SCR, also known as galvanic skin response) showed that higher levels of arousal were associated with generally higher response levels (Steiner and Barry, 2011, 2014). Thus, the SCR did not show response behavior as predicted by the BHT either, even though Eisenstein et al. (1991; 2012) illustrated the BHT with SCR data and SCRs were shown to exhibit classic criteria of habituation (Barry et al., 1993). Nevertheless, for other biological responses, the predictions of the BHT might still turn out to be valid. We think the here presented method of analyzing neurobehavioral data represents a sound way for verifying the predictions of the BHT.

Eisenstein et al. (2012) themselves also sought to support their theory empirically. Unfortunately, the selective averaging procedure used by Eisenstein et al. (2012) is, from our point of view, inconclusive: Participants were divided into those who showed an initial response decrease ('*habituaters*') and those who showed an initial response increase ('*sensitizers*'). Subsequently, the responses were averaged across the two sub-samples. However,

mathematically, such a division has to result in significant group differences in the average responses to S1 and S2. This is because both low S1 and strong S2 responses increase the likelihood for observing an initial response increase, whereas both strong S1 and low S2 responses increase the likelihood for observing an initial response decrease. In consequence, the pronounced differences between habituaters and sensitizers in their S1 and S2 responses, as described by Eisenstein et al. (2012), have to be considered as mere consequence of how the two sub-samples were defined. In contrast to Eisenstein et al. (2012), we inspected the possible interplay between habituation and sensitization in a within-subject approach. We think this approach provides a better operationalization of the central assumption of the BHT, namely that the *state* of alertness (and not its trait) is strongly associated with an individual's responsiveness. Furthermore, we consider our analysis as more powerful because every individual serves as his own control.

We acknowledge that the single-trial based quantification of the N100 amplitude has limited reliability due to the low signal-to-noise ratio of such data, even though the N100 component represents the most reliable AEP component (Näätänen and Picton, 1987). The currently used method for quantifying the N100 amplitude in single trials has the advantage that their average does correspond to the N100 amplitude in the AEP. Given this, the used method is very transparent and objective. On the other hand, slow potential shifts at baseline can influence N100 amplitude in single trials. In consequence, amplitude differences between the average AEPs to S1 across 'High $N1_{S1}$' and across 'Low $N1_{S1}$' trials were evident before and after the onset of the N100 (Fig. 1B). However, current findings indicate that the classification of the EEG data into 'High $N1_{S1}$' and 'Low $N1_{S1}$' trials was meaningful, as the post-stimulus theta and alpha activity was systematically larger for 'High $N1_{S1}$' trials than for 'Low $N1_{S1}$' trials even though the spectral content of the data was not taken into account for the classification of the trials. The relevance of theta oscillations for the magnitude of the N100 response has already previously been shown (e.g. Bruneau et al., 1993; Rosburg et al., 2009). The observed correlation between *z*-transformed theta post-stimulus activity and the *z*-transformed N100 amplitudes to S1 across all trials might be considered as further evidence for the validity of the current trial classification.

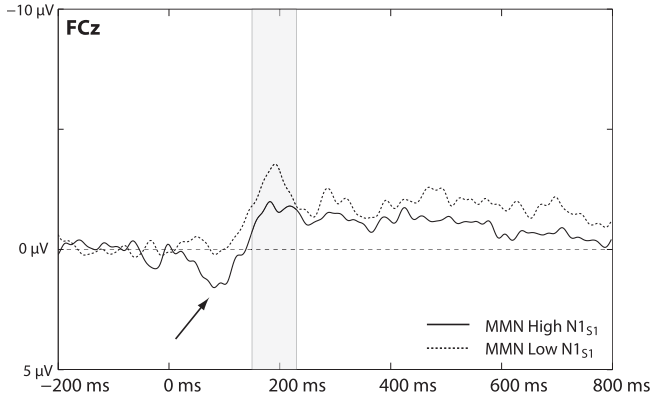

Fig. 3. The difference potential between the AEPs to deviants and standards. The latency range used for quantifying the MMN is marked by gray shading (150–230 ms). The arrow in this panel indicates the positive deflection in the N100 latency range that results from the differential N100 response for standard and deviant stimuli for 'High $N1_{S1}$' trials. The MMN was significantly larger for 'Low $N1_{S1}$' trials than for 'High $N1_{S1}$' trials.

4.3. Precursors of strong responses to S1

Levels of alertness and arousal at the time-point of stimulation were assumed to be reflected in the pre-stimulus theta and alpha activity. In contrast to the observed difference in post-stimulus theta and alpha activity between 'High $N1_{S1}$' and 'Low $N1_{S1}$' trials, pre-stimulus theta and alpha activity did not vary between the two kinds of trials. Thus, we found no evidence that the levels of alertness and arousal as reflected in these oscillations had an impact on the magnitude of the subsequent N100 responses. One might argue that the range of alertness within and across participants was simply too minimal to observe such effects since all participants were already used to the recording environment and watched an entertaining movie during the recordings.

The N100 component is diminished during sleep (e.g. Ogilvie et al., 1991). Yet, the N100 amplitude has sometimes not been

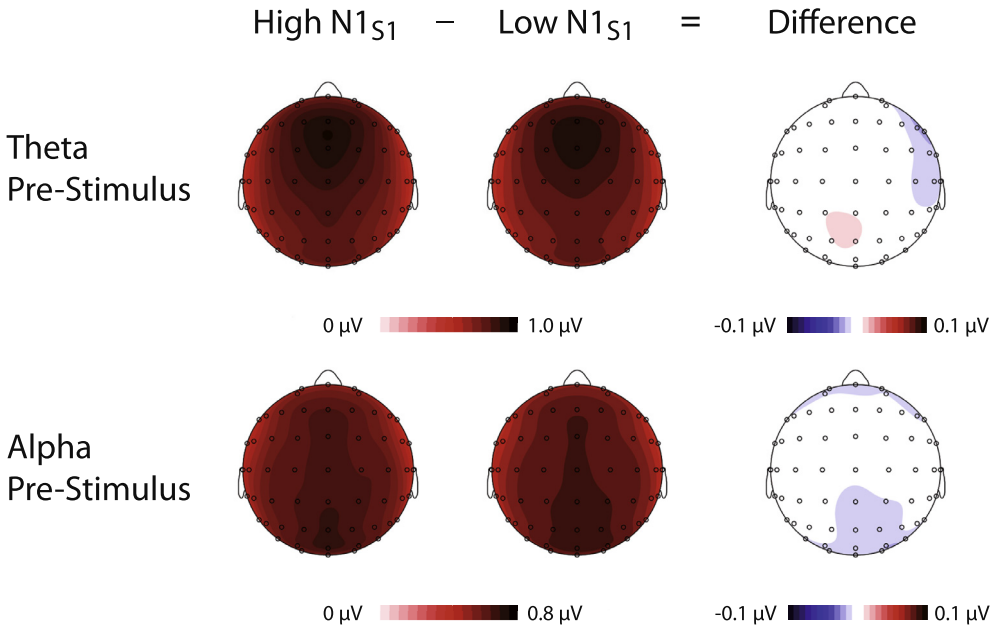

Fig. 4. The scalp distribution of the pre-stimulus theta and alpha activity (−500 ms to 0 ms) for the two subsamples of trials; no systematic variations between the two subsamples were observed.

Table 5
Pre- and post-stimulus frequency activity.

	Pre theta	Pre alpha	Post theta	Post alpha
$N1_{S1}$ low	0.93 (0.17)	0.65 (0.12)	1.07 (0.26)	0.68 (0.13)
$N1_{S1}$ high	0.92 (0.18)	0.65 (0.11)	1.30 (0.34)	0.73 (0.14)

The mean pre- and post-stimulus activity in the theta (4–8 Hz) and alpha (8.5–12 Hz) band in μV (±standard deviations) at FCz, for the separate trial samples (high vs. low N100 amplitudes to S1). There were no differences in the pre-stimulus activity between the two kinds of trials.

modulated by the transition from being awake to stage 1 sleep (Colrain et al., 2000). Similar to our finding, Colrain et al. (2000) reported that the N100 amplitude was not affected by alpha or theta state differences either. In contrast, De Blasio and Barry (2013a) found a direct relationship between the N100 amplitude and pre-stimulus theta activity, but no relationship between the N100 amplitude and pre-stimulus alpha activity (De Blasio and Barry, 2013b; De Blasio et al., 2013). Further studies are warranted to clarify what qualifies the brain state resulting in low or strong N100 responses. Delta activity (1–4 Hz) was not analyzed in the current study, because the chosen pre-stimulus interval was too short to reliably assess this low frequency activity. One previous study reported that high levels of pre-stimulus delta activity were associated with diminished N100 amplitudes (De Blasio and Barry, 2013b), but this was not confirmed in a second study (De Blasio et al., 2013).

4.4. Evidence for an interplay between sensitization and habituation in Muenssinger et al. (2013a)

In the study of Muenssinger et al. (2013a), fetal AEFs increased from S1 to S2 and subsequently decreased. As outlined above, Muenssinger and colleagues interpreted the initial increase as sensitization and the subsequent decrease as habituation. From our point of view, this interpretation is neither empirically nor theoretically justified. (1), to the best of our knowledge, there is no evidence that sensitization is a factor contributing to the response strength of AEF/AEP components after repeated stimulation. (2), the interpretation of Muenssinger et al. (2013a) does not take into account that habituation needs to be qualified by spontaneous recovery (criterion #2 for habituation, Rankin et al., 2009), i.e. the AEFs to the last stimulus of a train should be smaller than the AEFs to its 1st stimulus. This was neither the case for the AEFs of fetuses and newborns (Muenssinger et al., 2013a) nor was it the case for the AEFs of children at the age of 9–11 years (Muenssinger et al., 2013b). (3), a response decrease was not observed in newborns and children (Muenssinger et al., 2013a,b). If one assumes that the response decrease in fetuses (after S2) corresponds to the decrement (after S1) observed in adults it needs to be answered why such a decrease is absent in newborns and children. (4), Muenssinger et al. (2013a) did not take alternative explanations into account. We have previously noted that an initial response increase and subsequent decrease could simply be explained by a component overlap due to the short SOA used in that study (Rosburg, 2004), also due to the longer latencies for AEP components found in children (Ponton et al., 2002; Wunderlich et al., 2006). (5), Muenssinger and colleagues did not take the existing body literature into account. In the study of Muenssinger et al. (2013a), there is no reference to previous findings in adults at all. In the study of Muenssinger et al. (2013b), the misleading statement is made that "in the literature different characteristics are chosen to distinguish between habituation and sensory adaptation/fatigue and similar results are inconsistently discussed and interpreted (Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2010)" (p. 6). In fact, all three studies cited by Muenssinger et al. (2013b) consider the decrease of AEP/AEF components after repeated stimulation as not to be caused by habituation, and all three studies refer to the landmark paper of Thompson and Spencer (1966) that defined the criteria for habituation processes.

5. Conclusion

The analysis of AEP data averaged across all trials provided no evidence that habituation underlies the decrease of AEP components after stimulus repetition since major criteria of habituation were not met (no indication of an asymptotic decrease, response recovery, or dishabituation), as also reported in previous studies (e.g. Ritter et al., 1968; Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2006, 2010). Our study further sought to elucidate whether the response decrease of the AEP components N100 and P200 after stimulus repetition can be explained by an interplay between habituation and sensitization, as formulated by the BHT (Eisenstein et al., 2012). However, contrary to what is predicted by the BHT, the single trial analysis showed that initially large N100 responses were followed by likewise larger (and not weaker) N100 responses to S2 and standard tones (S2 to S4), as compared to trials with initially small N100 responses. Furthermore, we observed a differential processing of deviants in the two kinds of trials, again contrary to what is predicted by the BHT: In trials with an initially large N100, we observed a pronounced N100 amplitude decrease from standards to deviants, whereas no such decrease was present in trials with an initially small N100 responses. This finding cannot be reconciled with the view that the BHT serves the purpose of maximizing the organism's readiness to cope with new stimuli. In sum, we think that the refractoriness account provides a better explanation for the observed response behavior of AEP components after repeated stimulation.

Thus, impaired P50/N100/P200 suppression after repeated stimulation (as found in patients with schizophrenia in paired-click experiments) presumably indicates alterations of the refractoriness of neuronal networks generating these AEP responses. As outlined in the introduction, it is already problematic to equate such an impaired AEP response suppression to a deficiency of perceptual filter mechanisms (or 'sensory gating'), because the number of studies that actually have been able to establish a link between impaired P50/N100/P200 suppression and self-reported perceptual anomalies is as yet very limited (Micoulaud-Franchi et al., 2012, 2014; but: Jin et al., 1998; Johannesen et al., 2008). However, based on previous and current research, it is unsubstantiated to equate 'sensory gating' and 'habituation' (as prominent example: Chang et al., 2011). Such inappropriate labeling might give rise to misleading conclusions about functional impairments found in psychiatric and neurological patients. This is particularly important in consideration of clinical studies that aim at establishing impaired P50 suppression as neurophysiological endophenotype of schizophrenia (e.g. Johannesen et al., 2013), as well as in consideration of studies that aim at defining target receptors (such as the nicotinic acetylcholine receptors) for the treatment of cognitive symptoms in schizophrenia and use neurophysiological findings as guidance for drug developing (Tregellas, 2014; Rowe et al., 2015).

Acknowledgements

T.R. was financially supported by the German Research Foundation (DFG Ro 3533/1-1). The authors greatly appreciate the technical assistance of Michael Weigl, Julia Bock, and Nicole Recklies.

Conflict of interest: All funding resources supporting this study are acknowledged. The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.04.071.

References

Adler LE, Hoffer LJ, Griffith J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 1992;32:607–16.

Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150:1856–61.

Bak N, Rostrup E, Larsson HBW, Glenthøj BY, Oranje B. Concurrent functional magnetic resonance imaging and electroencephalography assessment of sensory gating in schizophrenia. Hum Brain Mapp 2014;35:3578–87.

Barry RJ. Stimulus significance effects in habituation of the phasic and tonic orienting reflex. Integr Physiol Behav Sci 2004;39:166–79.

Barry RJ, Cocker KI, Anderson JW, Gordon E, Rennie C. Does the N100 evoked potential really habituate? Evidence from a paradigm appropriate to a clinical setting. Int J Psychophysiol 1992;13:9–16.

Barry RJ, Feldmann S, Gordon E, Cocker KI, Rennie C. Elicitation and habituation of the electrodermal orienting response in a short interstimulus interval paradigm. Int J Psychophysiol 1993;15:247–53.

Barry R, Kirkaikul S, Hodder D. EEG alpha activity and the ERP to target stimuli in an auditory oddball paradigm. Int J Psychophysiol 2000;39:39–50.

Barry R, De Pascalis V, Hodder D. Preferred EEG brain states at stimulus onset in a fixed interstimulus interval auditory oddball task, and their effects on ERP components. Int J Psychophysiol 2003;47:187–98.

Barry RJ, Clarke AR, Johnstone SJ. Caffeine and opening the eyes have additive effects on resting arousal measures. Clin Neurophysiol 2011;122:2010–5.

Başar E, Stampfer HG. Important associations among EEG-dynamics, event-related potentials, short-term memory and learning. Int J Neurosci 1985;26:161–80.

Başar E, Demir N, Gönder A, Ungan P. Combined dynamics of EEG and evoked potentials. I. Studies of simultaneously recorded EEG-EPograms in the auditory pathway, reticular formation, and hippocampus of the cat brain during the waking stage. Biol Cybern 1979;34:1–19.

Bourbon WT, Will KW, Gary HE, Papanicolaou AC. Habituation of auditory event-related potentials: a comparison of self-initiated and automated stimulus trains. Electroencephalogr Clin Neurophysiol 1987;66:160–6.

Boutros NN, Trautner P, Rosburg T, Korzyukov O, Grunwald T, Schaller C, et al. Sensory gating in the human hippocampal and rhinal regions. Clin Neurophysiol 2005;116:1967–74.

Boutros NN, Gooding D, Sundaresan K, Burroughs S, Johanson C-E. Cocaine-dependence and cocaine-induced paranoia and mid-latency auditory evoked responses and sensory gating. Psychiatry Res 2006;145:147–54.

Boutros NN, Mears R, Pflieger ME, Moxon KA, Ludowig E, Rosburg T. Sensory gating in the human hippocampal and rhinal regions: regional differences. Hippocampus 2008;18:310–6.

Brandt ME, Jansen BH, Carbonari JP. Pre-stimulus spectral EEG patterns and the visual evoked response. Electroencephalogr Clin Neurophysiol 1991;80:16–20.

Bruneau N, Roux S, Guérin P, Garreau B, Lelord G. Auditory stimulus intensity responses and frontal midline theta rhythm. Electroencephalogr Clin Neurophysiol 1993;86:213–6.

Budd TW, Michie PT. Facilitation of the N1 peak of the auditory ERP at short stimulus intervals. Neuroreport 1994;5:2513–6.

Budd TW, Barry RJ, Gordon E, Rennie C, Michie PT. Decrement of the N1 auditory event-related potential with stimulus repetition: habituation vs. refractoriness. Int J Psychophysiol 1998;31:51–68.

Butler RA. Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. J Acoust Soc Am 1968;44:945–50.

Chang W-P, Arfken CL, Sangal MP, Boutros NN. Probing the relative contribution of the first and second responses to sensory gating indices: a meta-anaysis. Psychophysiology 2011;48:980–92.

Colrain IM, Di Parsia P, Gora J. The impact of prestimulus EEG frequency on auditory evoked potentials during sleep onset. Can J Exp Psychol 2000;54:243–54.

Crowley KE, Colrain IM. A review of the evidence for P2 being an independent component process: age, sleep and modality. Clin Neurophysiol 2004;115:732–44.

Davis H, Mast T, Yoshie N, Zerlin S. The slow response of the human cortex to auditory stimuli: recovery process. Electroencephalogr Clin Neurophysiol 1966;21:105–13.

De Blasio FM, Barry RJ. Prestimulus alpha and beta determinants of ERP responses in the Go/NoGo task. Int J Psychophysiol 2013a;89:9–17.

De Blasio FM, Barry RJ. Prestimulus delta and theta determinants of ERP responses in the Go/NoGo task. Int J Psychophysiol 2013b;87:279–88.

De Blasio FM, Barry RJ, Steiner GZ. Prestimulus EEG amplitude determinants of ERP responses in a habituation paradigm. Int J Psychophysiol 2013;89:444–50.

De Wilde OM, Bour LJ, Dingemans PM, Koelman JHTM, Linszen DH. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. Schizophr Res 2007;97:137–51.

Eisenstein EM, Eisenstein D. A behavioral homeostasis theory of habituation and sensitization: II. Further developments and predictions. Rev Neurosci 2006;17:533–57.

Eisenstein EM, Eisenstein D, Bonheim P. Initial habituation or sensitization of the GSR depends on magnitude of first response. Physiol Behav 1991;49:211–5.

Eisenstein E, Eisenstein D, Sarma J, Knapp H, Smith J. Some new speculative insights about the "behavioral homeostasis theory" as to how the simple learned behaviors of habituation and sensitization improve organism survival throughout phylogeny. Commun Integr Biol 2012;5:233–9.

Freedman R. A7-nicotinic acetylcholine receptor agonists for cognitive enhancement in schizophrenia. Annu Rev Med 2014;65:245–61.

Freedman R, Adler LE, Olincy A, Waldo MC, Ross RG, Stevens KE, et al. Input dysfunction, schizotypy, and genetic models of schizophrenia. Schizophr Res 2002;54:25–32.

Fruhstorfer H. Habituation and dishabituation of the human vertex response. Electroencephalogr Clin Neurophysiol 1971;30:306–12.

Fruhstorfer H, Soveri P, Järvilehto T. Short-term habituation of the auditory evoked response in man. Electroencephalogr Clin Neurophysiol 1970;28:153–61.

Fuentemilla L, Càmara E, Münte TF, Krämer UM, Cunillera T, Marco-Pallarés J, et al. Individual differences in true and false memory retrieval are related to white matter brain microstructure. J Neurosci 2009;29:8698–703.

Grau C, Fuentemilla L, Marco-Pallarés J. Functional neural dynamics underlying auditory event-related N1 and N1 suppression response. Neuroimage 2007;36:522–31.

Groves PM, Thompson RF. Habituation: a dual-process theory. Psychol Rev 1970;77:419–50.

Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernández G, Schaller C, et al. Neuronal substrates of sensory gating within the human brain. Biol Psychiatry 2003;53:511–9.

Haig AR, Gordon E. Prestimulus EEG alpha phase synchronicity influences N100 amplitude and reaction time. Psychophysiology 1998;35:591–5.

Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. Science 1973;182:177–80.

Jansen B, Brandt M. The effect of the phase of prestimulus alpha activity on the averaged visual evoked response. Electroencephalogr Clin 1991;80:241–50.

Ji B, Mei W, Zhang JX, Jing J, Wu Q, Zhuo Y, et al. Abnormal auditory sensory gating-out in first-episode and never-medicated paranoid schizophrenia patients: an fMRI study. Exp Brain Res 2013;229:139–47.

Jin Y, Bunney WE, Sandman CA, Patterson JV, Fleming K, Moenter JR, et al. Is P50 suppression a measure of sensory gating in schizophrenia? Biol Psychiatry 1998;43:873–8.

Johannesen JK, Bodkins M, O'Donnell BF, Shekhar A, Hetrick WP. Perceptual anomalies in schizophrenia co-occur with selective impairments in the gamma frequency component of midlatency auditory ERPs. J Abnorm Psychol 2008;117:106–18.

Johannesen JK, O'Donnell BF, Shekhar A, McGrew JH, Hetrick WP. Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder. Schizophr Bull 2013;39:1219–29.

Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 1999;29:169–95.

Klimesch W, Doppelmayr M, Russegger H, Pachinger T. Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 1996;7:1235–40.

Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 2007;53:63–88.

Knott V, de la Salle S, Smith D, Phillipe T, Dort H, Choueiry J, et al. Baseline dependency of nicotine's sensory gating actions: similarities and differences in low, medium and high P50 suppressors. J Psychopharmacol 2013;27:790–800.

Korzyukov O, Pflieger ME, Wagner M, Bowyer SM, Rosburg T, Sundaresan K, et al. Generators of the intracranial P50 response in auditory sensory gating. Neuroimage 2007;35:814–26.

Krasne FB, Teshiba TM. Habituation of an invertebrate escape reflex due to modulation by higher centers rather than local events. Proc Natl Acad Sci U S A 1995;92:3362–6.

Kurthen M, Trautner P, Rosburg T, Grunwald T, Dietl T, Kühn K-U, et al. Towards a functional topography of sensory gating areas: invasive P50 recording and electrical stimulation mapping in epilepsy surgery candidates. Psychiatry Res 2007;155:121–33.

Lagemann L, Okamoto H, Teismann H, Pantev C. Involuntary monitoring of sound signals in noise is reflected in the human auditory evoked N1m response. PLoS One 2012;7:e31634.

Lammertmann C, Fujiki N, Lütkenhöner B, Hari R. Short-term decrement of the auditory N1m response. In: Nenonen J, Ilmoniemi RJ, Katila T, editors. Biomag 2000, proceedings of 12th international conference on biomagnetism. Espoo: Helsinki University of Technology; 2001. p. 50–3.

Lijffijt M, Moeller FG, Boutros NN, Steinberg JL, Meier SL, Lane SD, et al. Diminished P50, N100 and P200 auditory sensory gating in bipolar I disorder. Psychiatry Res 2009;167:191–201.

Lucas M. Familiality of auditory evoked potentials: preliminary investigation of the auditory brainstem response and late latency cortical response. [Master thesis]. London, Ontario: University of Western Ontario; 2012.

Määttä S, Saavalainen P, Herrgård E, Pääkkönen A, Luoma L, Laukkanen E, et al. Event-related potentials to elementary auditory input in distractible adolescents. Clin Neurophysiol 2005;116:142–50.
Macdonald B, Barry RJ. Trial effects in single-trial ERP components and autonomic responses at very long ISIs. Int J Psychophysiol 2014;92:99–112.
Matuz T, Govindan RB, Preissl H, Siegel ER, Muenssinger J, Murphy P, et al. Habituation of visual evoked responses in neonates and fetuses: a MEG study. Dev Cogn Neurosci 2012;2:303–16.
Mayer AR, Hanlon FM, Franco AR, Teshiba TM, Thoma RJ, Clark VP, et al. The neural networks underlying auditory sensory gating. Neuroimage 2009;44:182–9.
Micoulaud-Franchi J-A, Aramaki M, Merer A, Cermolacce M, Ystad S, Kronland-Martinet R, et al. Toward an exploration of feeling of strangeness in schizophrenia: perspectives on acousmatic and everyday listening. J Abnorm Psychol 2012;121:628–40.
Micoulaud-Franchi J-A, Hetrick WP, Aramaki M, Bolbecker A, Boyer L, Ystad S, et al. Do schizophrenia patients with low P50-suppression report more perceptual anomalies with the sensory gating inventory? Schizophr Res 2014;157:157–62.
Muenssinger J, Matuz T, Schleger F, Kiefer-Schmidt I, Goelz R, Wacker-Gussmann A, et al. Auditory habituation in the fetus and neonate: an fMEG study. Dev Sci 2013a;16:287–95.
Muenssinger J, Stingl KT, Matuz T, Binder G, Ehehalt S, Preissl H. Auditory habituation to simple tones: reduced evidence for habituation in children compared to adults. Front Hum Neurosci 2013b;7:377.
Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987;24:375–425.
Näätänen R, Gaillard AW, Varey CA. Attention effects on auditory EPs as a function of inter-stimulus interval. Biol Psychol 1981;13:173–87.
Näätänen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I. "Primitive intelligence" in the auditory cortex. Trends Neurosci 2001;24:283–8.
Neylan TC, Fletcher DJ, Lenoci M, McCallin K, Weiss DS, Schoenfeld FB, et al. Sensory gating in chronic posttraumatic stress disorder: reduced auditory P50 suppression in combat veterans. Biol Psychiatry 1999;46:1656–64.
Ogilvie RD, Simons IA, Kuderian RH, MacDonald T, Rustenburg J. Behavioral, event-related potential, and EEG/FFT changes at sleep onset. Psychophysiology 1991;28:54–64.
Öhman A, Lader M. Selective attention and "habituation" of the auditory averaged evoked response in humans. Physiol Behav 1972;8:79–85.
Okamoto H, Kakigi R. Neural adaptation to silence in the human auditory cortex: a magnetoencephalographic study. Brain Behav 2014;1:1–9.
Pakarinen S, Takegata R, Rinne T, Huotilainen M, Näätänen R. Measurement of extensive auditory discrimination profiles using the mismatch negativity (MMN) of the auditory event-related potential (ERP). Clin Neurophysiol 2007;118:177–85.
Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, et al. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psychiatry Res 2008;158:226–47.
Pérez-González D, Malmierca MS. Adaptation in the auditory system: an overview. Front Integr Neurosci 2014;8:19.
Ponton C, Eggermont JJ, Khosla D, Kwong B, Don M. Maturation of human central auditory system activity: separating auditory evoked potentials by dipole source modeling. Clin Neurophysiol 2002;113:407–20.
Rahn E, Başar E. Enhancement of visual evoked potentials by stimulation during low prestimulus EEG stages. Int J Neurosci 1993;72:123–36.
Rankin CH, Abrams T, Barry RJ, Bhatnagar S, Clayton DF, Colombo J, et al. Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. Neurobiol Learn Mem 2009;92:135–8.
Ritter W, Vaughan HG, Costa LD. Orienting and habituation to auditory stimuli: a study of short term changes in average evoked responses. Electroencephalogr Clin Neurophysiol 1968;25:550–6.
Romani A, Callieco R, Cosi V. Prestimulus spectral EEG patterns and the evoked auditory vertex response. Electroencephalogr Clin Neurophysiol 1988;70:270–2.
Rosburg T. Effects of tone repetition on auditory evoked neuromagnetic fields. Clin Neurophysiol 2004;115:898–905.
Rosburg T, Trautner P, Korzyukov OA, Boutros NN, Schaller C, Elger CE, et al. Short-term habituation of the intracranially recorded auditory evoked potentials P50 and N100. Neurosci Lett 2004;372:245–9.
Rosburg T, Trautner P, Boutros NN, Korzyukov OA, Schaller C, Elger CE, et al. Habituation of auditory evoked potentials in intracranial and extracranial recordings. Psychophysiology 2006;43:137–44.
Rosburg T, Trautner P, Ludowig E, Helmstaedter C, Bien CG, Elger CE, et al. Sensory gating in epilepsy – effects of the lateralization of hippocampal sclerosis. Clin Neurophysiol 2008;119:1310–9.
Rosburg T, Trautner P, Fell J, Moxon KA, Elger CE, Boutros NN. Sensory gating in intracranial recordings-the role of phase locking. Neuroimage 2009;44:1041–9.
Rosburg T, Weigl M, Sörös P. Habituation in the absence of a response decrease? Clin Neurophysiol 2014;125:210–1.
Rosburg T, Zimmerer K, Huonker R. Short-term habituation of auditory evoked potential and neuromagnetic field components in dependence of the interstimulus interval. Exp Brain Res 2010;205:559–70.
Roth WT, Kopell BS. The auditory evoked response to repeated stimuli during a vigilance task. Psychophysiology 1969;6:301–9.
Rowe AR, Mercer L, Casetti V, Sendt K-V, Giaroli G, Shergill SS, et al. Dementia praecox redux: a systematic review of the nicotinic receptor as a target for cognitive symptoms of schizophrenia. J Psychopharmacol 2015;29:197–211.
Saenz M, Langers DRM. Tonotopic mapping of human auditory cortex. Hear Res 2014;307:42–52.
Sams M, Paavilainen P, Alho K, Näätänen R. Auditory frequency discrimination and event-related potentials. Electroencephalogr Clin Neurophysiol 1985;62:437–48.
Soininen HS, Karhu J, Partanen J, Pääkkönen A, Jousmäki V, Hänninen T, et al. Habituation of auditory N100 correlates with amygdaloid volumes and frontal functions in age-associated memory impairment. Physiol Behav 1995;57:927–35.
Sokolov EN. Perception and the conditioned reflex. London, UK: Pergamon Press; .
Sörös P, Knecht S, Manemann E, Teismann I, Imai T, Lütkenhöner B, Pantev C. Hemispheric asymmetries for auditory short-term habituation of tones? In: Nenonen J, Ilmoniemi RJ, Katila T, editors. Biomag 2000, proceedings of 12th international conference on biomagnetism. Espoo: Helsinki University of Technology; 2001. p. 47–9.
Sörös P, Michael N, Tollkötter M, Pfleiderer B. The neurochemical basis of human cortical auditory processing: combining proton magnetic resonance spectroscopy and magnetoencephalography. BMC Biol 2006;4:25.
Sörös P, Teismann IK, Manemann E, Lütkenhöner B. Auditory temporal processing in healthy aging: a magnetoencephalographic study. BMC Neurosci 2009;10:34.
Steiner GZ, Barry RJ. Exploring the mechanism of dishabituation. Neurobiol Learn Mem 2011;95:461–6.
Steiner GZ, Barry RJ. The mechanism of dishabituation. Front Integr Neurosci 2014;8:14.
Stigler SM. Regression towards the mean, historically considered. Stat Methods Med Res 1997;6:103–14.
Thoma RJ, Hanlon FM, Moses SN, Edgar JC, Huang M, Weisend MP, et al. Lateralization of auditory sensory gating and neuropsychological dysfunction in schizophrenia. Am J Psychiatry 2003;160:1595–605.
Thompson RF, Spencer WA. Habituation: a model phenomenon for the study of neuronal substrates of behavior. Psychol Rev 1966;73:16–43.
Tregellas JR. Neuroimaging biomarkers for early drug development in schizophrenia. Biol Psychiatry 2014;76:111–9.
Tregellas JR, Davalos DB, Rojas DC, Waldo MC, Gibson L, Wylie K, et al. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr Res 2007;92:262–72.
Tregellas J, Ellis J, Shatti S. Increased hippocampal, thalamic, and prefrontal hemodynamic response to an urban noise stimulus in schizophrenia. Am J Psychiatry 2009;166:354–60.
Turetsky BI, Dent G, Jaeger J, Zukin SR. P50 amplitude reduction: a nicotinic receptor-mediated deficit in first-degree relatives of schizophrenia patients. Psychopharmacology (Berl) 2012;221:39–52.
Ulanovsky N, Las L, Nelken I. Processing of low-probability sounds by cortical neurons. Nat Neurosci 2003;6:391–8.
Weiland BJ, Boutros NN, Moran JM, Tepley N, Bowyer SM. Evidence for a frontal cortex role in both auditory and somatosensory habituation: a MEG study. Neuroimage 2008;42:827–35.
Woods DL, Elmasian R. The habituation of event-related potentials to speech sounds and tones. Electroencephalogr Clin Neurophysiol 1986;65:447–59.
Wunderlich JL, Cone-Wesson BK, Shepherd R. Maturation of the cortical auditory evoked potential in infants and young children. Hear Res 2006;212:185–202.
Yadon CA. Three types of sensory gating: exploring interrelationships, individual differences, and implications [Ph.D. thesis]. Fort Collins, Colorado: Colorado State University; 2010.
Zhang F, Eliassen J, Anderson J, Scheifele P, Brown D. The time course of the amplitude and latency in the auditory late response evoked by repeated tone bursts. J Am Acad Audiol 2009;20:239–50.
Zhang F, Deshpande A, Benson C, Smith M, Eliassen J, Fu Q-J. The adaptive pattern of the auditory N1 peak revealed by standardized low-resolution brain electromagnetic tomography. Brain Res 2011;1400:42–52.