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

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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*

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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

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