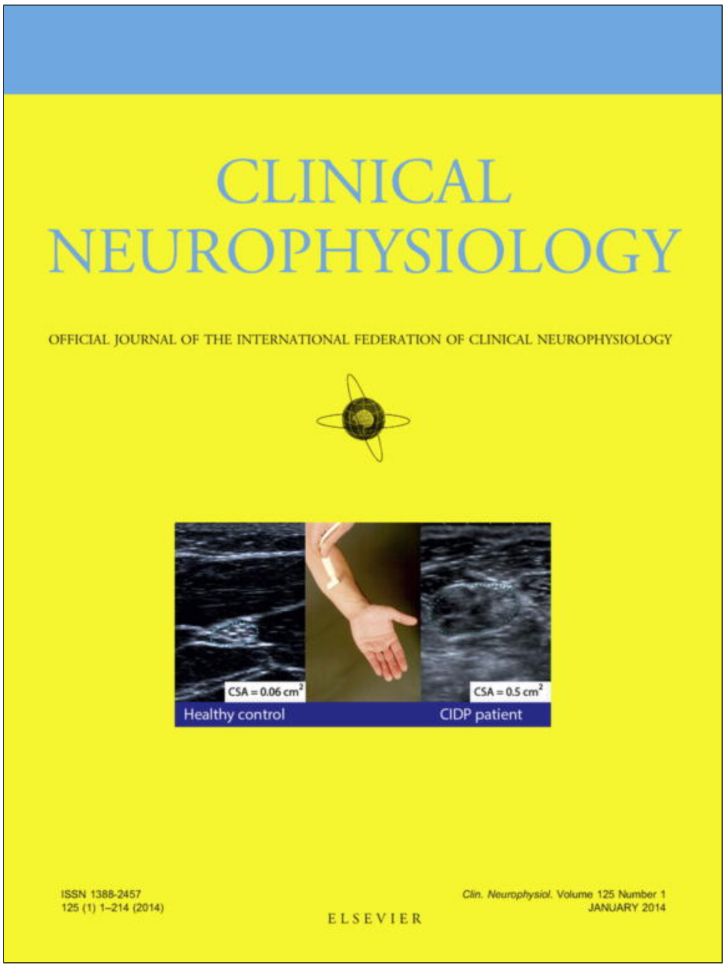

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Habituation in the absence of a response decrease?

In their magnetoencephalography (MEG) study, Muenssinger and colleagues investigated auditory evoked fields (AEFs) in fetuses and newborns (Muenssinger et al., 2013). The study aimed at qualifying the decrement of AEF signals to repeated stimulation as process of habituation and at describing developmental aspects of the decrement. Trains of identical tones with deviants at their 6th position were used as stimuli.

Similar stimulation procedures have previously been used when investigating the response decrement of auditory evoked potential (AEP) components in adults (e.g., Ritter et al., 1968; Fruhstorfer et al., 1970; Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2006; Sörös et al., 2009). Interestingly, Muenssinger et al. made no reference to any of such studies although they apparently adopted the stimulation procedure from these studies. However, the lack of reference is delicate for other reasons:

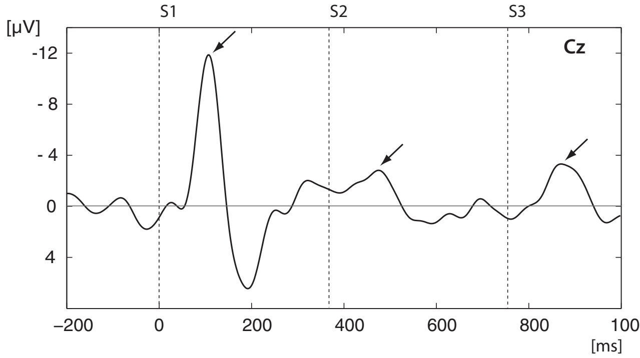

Fig. 1. The AEP in response to the first three tones of a stimulus train as recorded in an adult individual. The experimental set-up was identical to Muenssinger et al., but the ISI was minimally longer. Data were filtered from 1 to 15 Hz. The N100 as the most prominent AEP component is designated by arrows and the vertical dotted lines indicate the onset of the three tones (S1 to S3). The N100 amplitude shows a strong decrease after S1, like virtually all studies on adults (for review Rosburg et al., 2010). In contrast, no such decrease was observed by Muenssinger et al. The exemplary AEP data also illustrate the problem of using short ISIs: at the onset of S2, the AEP to S1 has not returned to baseline. In consequence, the exact quantification of the N100 and other AEP components to S2 is hampered. Note that the morphology of AEPs shows strong age-related changes during childhood (e.g., Ponton et al., 2002).

First, virtually all these previous studies on adults showed a strong response decrement of AEP components from the 1st to the 2nd stimulus of the train (Fig. 1; for review Rosburg et al., 2010). Such a response decrement occurred even when very short interstimulus intervals (ISIs) of 200 ms within the trains were used (Sörös et al., 2001). Yet, short ISIs (as they were also used by Muenssinger et al.) have the disadvantage that they tend to result in some unfavorable component overlap that in turn hampers the exact quantification of the response decrement.

Second, in order to define a response decrement as a process of habituation several criteria need to be fulfilled (Rankin et al., 2009), as also acknowledged by Muenssinger et al. Three criteria to be named here are: an asymptotic response decrease, stimulus specificity (response recovery to a different stimulus), and a subsequent response increase to re-presentation of the initial stimulus ('dishabituation') (Rankin et al., 2009). Previous AEP studies on adults revealed that the criteria of an asymptotic decrease and dishabituation were not met (Barry et al., 1992; Budd et al., 1998; Rosburg et al., 2010); this led the authors of these studies to the conclusion that habituation as mechanism behind the short-term decrement of AEP components is questionable.

In contrast, Muenssinger et al. claim that auditory habituation is present in the fetus: Their prime argument is that they observed a response decrease of the root mean square (RMS) of the recorded AEF from the 2nd to the 5th stimulus in the fetus group (but not in the neonatal group). Consideration of previous studies on adults would have shown that blanking out the response behavior from 1st to 2nd stimulus and focusing exclusively on the response decrement from the 2nd to the 5th stimulus are completely arbitrary and in no way justifiable on a theoretical level. If anything is remarkable about the response behavior of the AEF signal to repeated stimulation in the study of Muenssinger et al. it is the *absence* of a response decrement after the 1st stimulus in both samples.

Given that the principal criterion for habituation, namely that of a response decrease, is not fulfilled, it is difficult to understand on what empirical basis Muenssinger et al. make their claim that they observed habituation in the fetus. The presence of dishabituation would naturally provide strong support for this claim. However, there was no such response increase after the presentation of the deviating stimulus either.

We acknowledge that Muenssinger et al. presumably show a larger response to the deviating sound than to the standard stimuli. Thus, at least one of the three named criteria for habituation appears to be met. However, what the authors miss is that the larger response to the deviating stimulus might be interpreted much better in terms of recovery from neural refractoriness than in terms of habituation (Butler, 1968; Budd et al., 1998), given that other criteria of habituation were not met. In short, on the basis of the refractoriness account one would conclude that the magnitude of AEFs to deviants is larger than the AEFs to standards because the intervals between deviants are longer than the intervals between standards.

The concept of refractoriness is not mentioned by Muenssinger et al. although it also needs to be taken into account when interpreting the mismatch negativity (MMN), as recorded in their study. The MMN is commonly calculated as difference potential (AEP to deviants – AEPs to standards). The idea behind this subtraction procedure is that the obligatory sensory response is subtracted from the AEP to deviants and only genuine MMN activity, reflecting the outcome of a memory-comparison mechanism, is left. However, if the pitch difference between standard and deviant is large, the subtraction procedure does not work properly anymore, because the refractory state of neurons generating the obligatory sensory response is not the same for standards and deviants. This leads to a contamination of genuine MMN activity with activity reflecting the sensory processing of deviants. The opposite way around, the quantification of sensory responses can be contaminated by MMN-related activity, as well.

Such contaminations are detectable to some extent in AEPs with good signal-to-noise ratios by latency differences (MMN follows the main AEP component N100 and precedes P3a activity); this issue is much more complicated when AEPs are noisy, as it is unfortunately the case for recordings in neonatal and fetus populations. For avoiding such contaminations of the MMN signal, a core guideline recommends using small pitch differences between standards and deviants (Duncan et al., 2009). On the basis of the provided information, we do not know how Muenssinger et al. disentangled AEF components reflecting sensory processing and AEF components reflecting deviance detection (MMN, P3a) because the authors neither show average waveforms, nor do they describe temporal aspects of the recorded signals but the MMN latency.

Taken together, we argue that the study of Muenssinger et al. provides no empirical evidence for short-term habituation in fetuses and newborns. We have similar objections with regard to a previous study of the same group that claimed the presence of habituation in the visual modality for this age group (Matuz et al., 2012). In this report, the response recovery after presentation of a deviating stimulus *and* a long interval of no stimulation has misleadingly been qualified as dishabituation. Clearly, more research is needed to understand the mechanisms behind the short-term decrement of evoked potentials after repeated stimulation. Yet, for a better understanding of these mechanisms it is little helpful to qualify any behavior that shows a response decrement or behavior that does not even show a response decrement as habituation.

References

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.

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.

Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Näätänen R, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol 2009;120:1883–908.

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

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.

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 2013;16:287–95.

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.

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.

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, 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.

Sörös P, Knecht S, Manemann E, Teismann I, Imai T, Lütkenhöner B, et al. Hemispheric asymmetries for auditory short-term habituation of tones? In: Nenonen J, Imoniemi RJ, Katila T, editors. Proceedings of 12th international conference on biomagnetism biomag 2000, Espoo: Helsinki University of Technology; 2001. p. 47–49.

Sörös P, Teismann IK, Manemann E, Lütkenhöner B. Auditory temporal processing in healthy aging: a magnetoencephalographic study. BMC Neurosci 2009;10:34.

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