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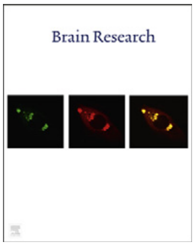

Research Report

Repetition suppression of the rat auditory evoked potential at brief stimulus intervals

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ABSTRACT

An important prerequisite for the development of animal models of human auditory evoked potentials (AEP) is the accurate identification of homology. Prior research has revealed some remarkably similar response properties between rat and human AEPs, although there remains little consensus regarding the nature or validity of this correspondence. In the present study we seek to extend this research by examining the response properties of rat AEP as a function of stimulus repetition and interval. The aim being to determine whether rat AEP components show the same paradoxical reversal of repetition suppression observed for the human N100 AEP component at brief stimulus intervals. To achieve this, AEPs were recorded epidurally at the vertex in the freely moving rat in response to acoustic stimuli presented at random stimulus intervals between 50 and 5000 ms. Using stimulation and analysis techniques to remove AEP waveform distortion due to overlapping AEP responses, the present results show that rat AEP components can be successfully resolved at intervals as brief as 50 ms. The results also demonstrate several fundamental types of correspondence between human and rat AEP components in terms of the sensitivity to stimulus interval and acoustic stimulus type. However the results found no evidence that rat AEP components show the reversal of repetition suppression at brief, relative to long, stimulus intervals as demonstrated for the N100 component in humans. The results are discussed in terms of EEG recording and AEP analysis procedures that provide promising avenues for future research.

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1. Introduction

Prior rat auditory evoked potential (AEP) research has identified several remarkable commonalities between the human and rat AEPs (see Shaw, 1988 for review). Similar to the scalp-recorded AEP in humans and other mammals, the AEP recorded from the surface of the cortex (epidural) of rats is elicited by a wide range of acoustic stimuli, is polyphasic in nature and consists of a reproducible sequence of positive and negative peaks (i.e. components) reflecting neural activity at different levels of the ascending auditory system from brainstem to cortex (Knight et al., 1985).

1.1. *AEP response suppression following stimulus repetition*

Adaptation is a ubiquitous phenomenon in all cortical sensory systems and can be broadly defined as the suppression of a neural or behavioural response to a repeated stimulus. As such, AEP response suppression is thought to reflect a reduction of redundant cortical processing of the repeated stimulus as well as increasing sensitivity to a new stimulus (i.e. sensory specific adaptation or SSA) (Antunes et al., 2010). The fundamental nature of adaptation provides a potential means to better clarify the correspondence between human and rat AEPs by determining the relative influence of stimulus repetition and interval on AEP components across species.

It is well established that both middle latency (P50) and long latency AEP components (N100 and P200) in humans are suppressed following stimulus repetition (see Naatanen and Picton, 1987 for review). This repetition suppression is largely determined by the length of the silent interval (inter-stimulus interval or ISI), showing a positive exponential function of ISI for intervals between 1 and 16 s (Ritter et al., 1968; Hari et al., 1982; Budd et al., 1998; Rosburg et al., 2010). Similarly, the rat N50 AEP component shows repetition suppression for a number of different stimulation procedures (Adler et al., 1986; de Bruin et al., 2001; Knight et al., 1985; Campbell et al., 1995; Boutros et al., 1997; Sambeth et al., 2004). The rat N50 is also strongly dependent on ISI, showing an exponential increase in amplitude with increasing ISI reaching an asymptote at 5 s ISIs (Dafny, 1975). These response properties are also broadly consistent with the proposal that the N50 is homologous to the human N100 component (Knight et al., 1985), which also shows a midline/vertex topography and dominates the scalp recorded human AEP under passive stimulation conditions.

Despite this correspondence between the rat N50 and human N100, several authors have questioned whether there is adequate evidence to support this homology (de Bruin et al., 2001; Sambeth et al., 2003, 2004). Some have proposed that the rat N50 is equivalent to the human P50 (Adler et al., 1982, 1986; Boutros et al., 1997; Boutros and Kwan, 1998) whereas others suggest that the rat P13 is the equivalent of the human P50 (Miyazato et al., 1999), or that the earlier mid latency rat AEP components P17 and N22 show response properties more consistent with the human P50 (de Bruin et al., 2001). While the lack of standardised stimulation and recording procedures in rat studies undoubtedly contributes to this lack of consensus (de Bruin et al., 2001; Sambeth et al., 2003, 2004), the primary obstacle to clarifying the correspondence between rat and human AEPs is that multiple AEP components in both species show interval dependent response suppression.

1.2. *AEP response enhancement following repetition at brief ISIs*

The paradoxical reversal of N100 repetition suppression observed in humans when stimulus interval is decreased below 300 ms (Loveless et al., 1989; Budd and Michie, 1994) may provide a means to identify a rat homologue of the human N100, since this reversal does not occur for the other major human AEP components (Loveless et al., 1996; McEvoy et al., 1997; Zacharias et al., 2012). While most prior rat AEP studies have generally not used stimulus intervals less than 300 ms, most likely to avoid AEP distortion due to overlapping responses, Knight et al. (1985) used stimulation rates as rapid as 8 Hz but reported no evidence of amplitude increases for any of the middle or long latency rat AEP components. Similarly, Campbell et al. (1995) used stimulation rates as fast as 4 Hz and found no evidence or amplitude increases relative to slower stimulation rates. de Bruin et al. (2001) used blocks of paired-stimulus presentations at regular ISIs (within each ISI condition) and found no evidence of AEP components increases at the shortest ISI used (200 ms). However an important limitation for these rat AEP studies has been the failure to address AEP response distortion when using such fast stimulation rates.

The aim of the present study was to extend prior research examining the correspondence between human and rat AEP components by determining whether rat AEP components show a reversal of the traditional positive AEP/ISI function at brief relative to longer stimulus intervals. Based on similar studies in humans, the present study employed a randomised irregular sequence of stimulus intervals between 50 ms and 5 s, together with the ADJAR correction procedure (Woldorff, 1993) to correct for AEP overlap at brief stimulus interval. To determine whether the variable effects of ISI on rat AEP components found in prior studies reflect differences in acoustic stimuli employed, the present study used both pure tone and broadband noise stimuli in separate sessions to assess the influence of ISI on the rat AEP.

2. Results

Fig. 1 shows the ADJAR grand average AEPs separately for tone and noise stimuli averaged across all ISIs used in the present experiment. For the grand average AEP waveforms (average across all ISI ranges), the ADJAR correction waves for both stimuli reveal very little distortion due to AEP response overlap and hence, little apparent difference between the uncorrected and corrected Grand Average AEPs. This results from the relatively wide ISI ‘jitter’ (50–5000 ms) used in the present study and indicates that the corrected grand average AEP provides a relatively undistorted estimate of AEP response distortion as required for the ADJAR correction of