Hearing Research 302 (2013) 50–59

Contents lists available at SciVerse ScienceDirect

Hearing Research

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

Research paper

Auditory evoked magnetic fields in individuals with tinnitus

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ARTICLE INFO

Article history:
Received 18 August 2012
Received in revised form
11 April 2013
Accepted 16 April 2013
Available online 29 April 2013

ABSTRACT

Some forms of tinnitus are likely to be perceptual consequences of altered neural activity in the central auditory system triggered by damage to the auditory periphery. Animal studies report changes in the evoked responses after noise exposure or ototoxic drugs in inferior colliculus and auditory cortex. However, human electrophysiological evidence is rather equivocal: increased, reduced or no difference in N1/N1m evoked amplitudes and latencies in tinnitus participants have been reported.

The present study used magnetoencephalography to seek evidence for altered evoked responses in people with tinnitus compared to controls (hearing loss matched and normal hearing) in four different stimulus categories (a control tone, a tone corresponding to the audiometric edge, to the dominant tinnitus pitch and a tone within the area of hearing loss). Results revealed that amplitudes of the evoked responses differed depending on the tone category. N1m amplitude to the dominant tinnitus pitch and the frequency within the area of hearing loss were reduced compared to the other two categories. Given that tinnitus pitch is typically within the area of hearing loss, the differences in the evoked responses pattern in tinnitus participants seem to be related more to the hearing loss than to the presence of tinnitus.

1. Introduction

Recent theories postulate that some forms of tinnitus are a perceptual consequence of altered neural activity in the central auditory system triggered by damage to the auditory periphery whereby the abnormal activity along the auditory pathway is erroneously interpreted as a sound (Eggermont and Roberts, 2004). While loss of afferents following cochlear damage may be the initiating cause in the peripheral system, central mechanisms are probably crucial for maintaining tinnitus. Animal studies have provided a wealth of evidence in favour of this view and have been the main source of our current knowledge regarding neurophysiological correlates of tinnitus (for a recent review see Noreña, 2011). In addition to reduced output from the cochlea and auditory nerve after noise exposure or ototoxic drugs, many animal studies have observed concomitant changes in the ascending auditory pathway both at rest (spontaneous activity) and in response to external sounds (evoked activity). Following sensory deafferentation after noise trauma or ototoxic drugs neurons within the central auditory system can become hyperexcitable. For example, at the level of auditory cortex increased sound-evoked firing rate has been shown after noise exposure in cats (Kimura and Eggermont, 1999; Noreña et al., 2003) and those activity changes appeared to be greatest for frequencies below the hearing loss (Noreña et al., 2003). The amplitude of the sound-evoked response has generally been shown to increase after noise exposure in the auditory cortex of chinchillas (Salvi et al., 2000), cats (Noreña et al., 2003), guinea pigs (Popelar et al., 1987; Syka et al., 1994) and rats (Syka and Rybalko, 2000; Popelar et al., 2008; Sun et al., 2008).

Several mechanisms have been proposed to explain changes in the evoked responses associated with tinnitus. One view proposes an unmasking of the excitatory activity due to loss of lateral inhibition as a result of hearing loss (Gerken, 1996). A second pervasive model gives primacy to the notion that cochlear damage results in the reorganisation of the tonotopic map in central auditory

Abbreviations: ABR, auditory brainstem responses; ANOVA, analysis of variance; EEG, electroencephalography; HL, hearing loss; MEG, magnetoencephalography; PTA, pure tone average; SL, sensation level; TI, tinnitus; THI, Tinnitus Handicap Inventory.

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0378-5955
http://dx.doi.org/10.1016/j.heares.2013.04.006

structures so that neurons at the audiometric edge of the hearing loss acquire the characteristic frequency of their unaffected neighbouring areas. As a consequence, more neurons respond to the frequency at the edge and a resulting enhancement of the evoked response to that frequency can be observed (Robertson and Irvine, 1989; Rajan et al., 1993). More recent models postulate increased spontaneous neuronal activity corresponding to the hearing loss region through homeostatic plasticity (Noreña, 2011; Schaette and Kempter, 2006). Homeostatic plasticity is postulated to stabilise the neural activity in cases of auditory deprivation by scaling up the strength of excitatory synapses and scaling down the strength of inhibitory synapses, which results in increased excitability of neurons. Empirical evidence for this is lacking in humans, but recent data using auditory brainstem responses (ABR), showed reduction of wave I and normalisation of wave V in participants with tinnitus and normal hearing in comparison to normal-hearing controls (Schaette and McAlpine, 2011).

Whatever the precise neural mechanism for tinnitus, the implication for human neuroimaging studies using electroencephalography (EEG) or magnetoencephalography (MEG) is that an increase in neural excitability probably elevates the amplitude of the sound-evoked response, and possibly also affects its latency. Moreover, we might expect differences in the amplitude and/or latency of the evoked responses to predominantly affect either the edge frequency of the hearing loss and/or a frequency corresponding to the dominant tinnitus pitch relative to a control tone that falls within the region of normal hearing. The N1 (EEG) or N1m (MEG) component of the auditory evoked response would seem relevant for studying tinnitus-related activity because it is a reliable cortical response that reflects stimulus properties such as frequency (Näätänen and Picton, 1987). The characteristics of the N1/N1m are also purported to reflect auditory selective attention (Näätänen and Picton, 1987), which is also thought to play a role in tinnitus (e.g., Gu et al., 2010; Hallam et al., 2004). In normal-hearing people, the N1 amplitude typically decreases as a function of frequency (Naka et al., 1999; Fujioka et al., 2002; Gabriel et al., 2004) while changes in latency are usually less pronounced and different studies report mixed results (Roberts and Poeppel, 1996; Naka et al., 1999; Gabriel et al., 2004).

Previous studies have investigated the N1/N1m response as a correlate of tinnitus, but these have yielded rather inconsistent results. A number of studies have predicted generalised hyperexcitability, testing this question by measuring activity evoked by a low-frequency tone (often 1 kHz) corresponding to the region of normal hearing thresholds. Hoke et al. (1989, 1998) used MEG to demonstrate enhanced amplitude of N1m response in people with lateralised tinnitus and hearing loss compared to normally hearing controls, with no difference in N1m latency. Weisz et al. (2005) reported similar group amplitude differences for a low-frequency tone (one octave below the audiometric edge frequency), but this difference was limited to the right hemisphere only. The case study by Pantev et al. (1989) is broadly consistent with these results. As the patient recovered from tinnitus over an 8-month period, N1m decreased in amplitude, while latency remained unchanged. In contrast, Attias et al. (1993) found reduced N1 amplitude for the tinnitus group compared to hearing-matched controls using EEG. Similarly, Jacobson and McCaslin (2003) showed that people with tinnitus demonstrated significantly smaller N1 amplitudes for 0.5 and 1 kHz tones than normally hearing controls, despite these frequencies being in the region of normal auditory sensitivity for both groups. While neither of these EEG studies reported a group difference in N1 latency, Noreña et al. (1999) found that N1 latencies in participants with bilateral tinnitus were shorter than those in hearing-matched controls, but only at the highest sound intensities (80 and 90 dB SPL). However, it is difficult to draw any conclusions about absolute amplitude of N1 component alone because Noreña et al. (1999) report only the difference between N1 and P2 components. Several MEG studies using 1-kHz tones have failed to find any systematic differences between N1m for people with tinnitus and normally hearing controls in either evoked amplitude or latency (Jacobson et al., 1991; Colding-Jorgensen et al., 1992).

A prediction from the viewpoint of tonotopic reorganisation is that there should be an enhanced response to a frequency corresponding to the audiometric edge of a sloping high-frequency hearing loss. One MEG study found a significant increase of cortical strength values (dipole moments) for the audiometric edge frequency compared to lower frequencies in people with hearing loss, with seven out of eight of these also experiencing tinnitus (Dietrich et al., 2001). These authors postulate that this effect is due to expansion of the cortical representation of the edge frequency. However, it is uncertain whether this frequency-specific effect is a marker for tinnitus because a subsequent study found no between-group differences in N1m dipole strength or N1m latency for a frequency corresponding to the audiometric edge (tinnitus with hearing loss versus normally hearing controls, Weisz et al., 2005).

Other studies have sought evidence for enhanced responses corresponding to the tinnitus frequency, which is often within the region of hearing loss, by investigating intensity dependence of a tone corresponding to the dominant tinnitus pitch (Kadner et al., 2002; Pineda et al., 2008). They postulated that tinnitus-related activity would produce an increase in neuronal firing rate or activation of a greater neural substrate, which would result in enhanced intensity dependence of the responses to tones at the tinnitus frequency. Kadner et al. (2002) found that, in tinnitus subjects with hearing loss, responses to the tinnitus frequency were slightly more intensity dependent, with steeper intensity response curves, while responses to 2-kHz tones (approximately one octave below the tinnitus frequency) were slightly less intensity dependent than in normally hearing controls (less steep intensity response curve). The authors suggested that this is due to lateral inhibition caused by tinnitus-related activity. In agreement with the above study, Pineda et al. (2008) demonstrated decreased intensity dependence of responses to the tinnitus frequency after three weeks of customised sound therapy in tinnitus patients, making these responses more similar to controls. They proposed that higher slopes of intensity functions in tinnitus patients indicate reorganisation of the cortical tonotopic map, which might be reversed with customised sound therapy.

In addition to the N1m, some of the above MEG studies have also analysed the P2m response (Hoke et al., 1989, 1998; Jacobson et al., 1991; Colding-Jorgensen et al., 1992; Noreña et al., 1999). Some of these studies that found differences between tinnitus participants and controls with a reduced P2/P2m component in tinnitus subjects (Hoke et al., 1989, 1998; Attias et al., 1993). However, it is noteworthy that Jacobson et al. (1991) reported that the P2m component was often absent in control participants. In most individuals (22 out of 25) P2m was reduced and this resulted in a P2m/N1m ratio below the 0.5 value that Hoke et al. (1989) used as a lower limit of their objective classification criterion for having tinnitus. It is possible that the orientation of the P2m generators relative to the MEG sensors render the imaging technique rather weakly sensitive for detecting this component of the evoked signal. Indeed, EEG seems more sensitive than MEG in detecting the P2 component as all participants in the above study demonstrated normal P2 in EEG recordings (Jacobson et al., 1991). For this reason, the present study assessed the N1m component alone; the most reliable evoked component to be seen in individual listeners.

There are several major challenges to consolidating the outcomes from the different studies. First, authors chose to present different stimulating tones; corresponding to a normal hearing