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Research paper

Evidence for differential modulation of primary and nonprimary auditory cortex by forward masking in tinnitus

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ABSTRACT

It has been proposed that tinnitus is generated by aberrant neural activity that develops among neurons in tonotopic of regions of primary auditory cortex (A1) affected by hearing loss, which is also the frequency region where tinnitus percepts localize (Eggermont and Roberts 2004; Roberts et al., 2010, 2013). These models suggest (1) that differences between tinnitus and control groups of similar age and audiometric function should depend on whether A1 is probed in tinnitus frequency region (TFR) or below it, and (2) that brain responses evoked from A1 should track changes in the tinnitus percept when residual inhibition (RI) is induced by forward masking. We tested these predictions by measuring (128-channel EEG) the sound-evoked 40-Hz auditory steady-state response (ASSR) known to localize tonotopically to neural sources in A1. For comparison the N1 transient response localizing to distributed neural sources in nonprimary cortex (A2) was also studied. When tested under baseline conditions where tinnitus subjects would have heard their tinnitus, ASSR responses were larger in a tinnitus group than in controls when evoked by 500 Hz probes while the reverse was true for tinnitus and control groups tested with 5 kHz probes, confirming frequency-dependent group differences in this measure. On subsequent trials where RI was induced by masking (narrow band noise centered at 5 kHz), ASSR amplitude increased in the tinnitus group probed at 5 kHz but not in the tinnitus group probed at 500 Hz. When collapsed into a single sample tinnitus subjects reporting comparatively greater RI depth and duration showed comparatively larger ASSR increases after masking regardless of probe frequency. Effects of masking on ASSR amplitude in the control groups were completely reversed from those in the tinnitus groups, with no change seen to 5 kHz probes but ASSR increases to 500 Hz probes even though the masking sound contained no energy at 500 Hz (an “off-frequency” masking effect). In contrast to these findings for the ASSR, N1 amplitude was larger in tinnitus than control groups at both probe frequencies under baseline conditions, decreased after masking in all conditions, and did not relate to RI. These results suggest that aberrant neural activity occurring in the TFR of A1 underlies tinnitus and its modulation during RI. They indicate further that while neural changes occur in A2 in tinnitus, these changes do not reflect the tinnitus percept. Models for tinnitus and forward masking are described that integrate these findings within a common framework.

Abbreviations: A1, Primary Auditory Cortex; A2, Nonprimary Auditory Cortex; AM, Amplitude Modulated; ASSR, Auditory Steady-State Response; BPN, Band Pass Noise; CF, Center Frequency; EEG, Electroencephalogram; M, Masking Condition; MEG, Magnetoencephalography; NM, No Masking Condition; N1, N1 Transient Response; RI, Residual Inhibition; TFR, Tinnitus Frequency Region; THQ, Tinnitus Handicap Questionnaire

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1. Introduction

Most cases of persistent tinnitus are associated with hearing loss expressed either in the audiogram or detected by more sensitive measures. When subjects with audiometric hearing loss are asked to rate several sound frequencies for similarity to their tinnitus, similarity judgments typically commence near the edge of normal hearing in the audiogram and increase in proportion with the depth of hearing loss, comprising a tinnitus frequency region (TFR) spanning the hearing impaired region (Noreña et al., 2002; Roberts et al., 2006). Band-pass masking sounds that produce a brief forward suppression of tinnitus (called "residual inhibition" or RI) do so optimally in proportion to the extent to which their center frequencies (CFs) are also in the same frequency region (Roberts et al., 2008; Roberts, 2010). These psychoacoustic findings, which describe tinnitus associated with audiometric notches as well as sloping hearing loss (reviewed by Eggermont and Roberts, 2014), suggest that aberrant neural processes taking place in the hearing loss region of central auditory structures contribute to tinnitus while disrupting these processes with a masker suppresses it. Tinnitus appearing with a clinically normal audiogram (these cases constituting a minority of tinnitus cases) may not represent exceptions to this principle. Electrophysiological (Schaette and McAlpine, 2011; Gu et al., 2012) and psychoacoustic (Hébert et al., 2013) evidence suggests that such cases may involve damage to high threshold auditory nerve fibers (ANFs) not detected by the audiogram. The high-threshold ANFs most vulnerable to damage by noise exposure (Furman et al., 2013) or to deterioration with aging (Sergeyenko et al., 2013) are those with high frequency tuning (Kujawa and Liberman, 2009), which is consistent with the percepts reported in audiometrically normal tinnitus (Roberts et al., 2008; Schaette and McAlpine, 2011). Cochlear factors may also explain why not all individuals with high frequency hearing loss detected by the audiogram develop tinnitus (Tan et al., 2013). High threshold ANFs with high frequency tuning could be better preserved in such individuals, although this question has not been extensively studied.

Neural changes produced by putative tinnitus-inducing noise trauma in animals include (i) increased spontaneous firing of neurons in cortical (Noreña and Eggermont, 2003, 2006) and subcortical (Bauer et al., 2008 Brozoski et al., 2002; Kaltenbach et al., 2004; Mulders and Robertson, 2011; Vogler et al., 2014; Koehler and Shore, 2013a,b; Kalappa et al., 2014) auditory structures; (ii) increased synchronous activity among neurons in tonotopic regions of primary auditory cortex (A1) affected by hearing loss (Noreña and Eggermont, 2003; Seki and Eggermont, 2003; Engineer et al., 2011); (iii) reduced inhibition in the auditory cortex (Yang et al., 2011); (iv) increased gain in deafferented central auditory pathways (Engineer et al., 2011; Kalappa et al., 2014; Stefanescu, in press); and (v) shifts in the tuning preferences of auditory cortical neurons such that sound frequencies near the edge of normal hearing come to be overrepresented in the cortical tonotopic map (Robertson and Irvine, 1989; Rajan et al., 1993; Noreña and Eggermont, 2003). Behavioral and functional imaging studies of human tinnitus sufferers have corroborated increased gain in central pathways (Hébert et al., 2013; Gu et al., 2012; Schaette and McAlpine, 2011), reduced inhibition in the auditory cortex (Diesch et al., 2010b), and cortical map reorganization in A1, the latter at least when hearing loss is present (Wienbruch et al., 2006). Auditory cortical regions known to be sensitive to attention (Paltoglou et al., 2009) also appear to be persistently activated in humans experiencing tinnitus (Lanting et al., 2009; Gu et al., 2010; Roberts et al., 2013), which may explain deficits in the modulation of attention observed in such subjects (Cuny et al., 2004; Paul et al., 2014). Magnetoencephalography (MEG) studies have observed increased slow (<4 Hz; Weisz et al., 2005, 2007; Adjamian et al., 2012) and alpha (8–12 Hz; Weisz et al., 2005, 2007) oscillations in the auditory cortex of tinnitus subjects, as well as increased gamma oscillations (>40 Hz; Weisz et al., 2007) that may reflect changes in synchronous neural network activity associated with tinnitus percepts. Of the numerous neural changes reviewed here, hypersynchrony occurring in the TFR of A1 has been proposed by some models (Eggermont and Roberts, 2004; Roberts et al., 2013; also see Weisz et al., 2007) to be the proximal neural source of tinnitus. Another potential correlate (increased spontaneous firing) has been observed to occur below as well as within the hearing loss region of A1 in animals exposed to noise trauma, while increased synchronous activity is confined largely to the hearing loss region, which is where tinnitus percepts localize in humans.

In contrast to the aforementioned studies which have examined neural changes believed to accompany the experience of tinnitus, the experiment reported in this paper examined neural changes that occur when tinnitus is suppressed during RI. To achieve this aim, we contrasted sound-evoked brain activity between a baseline condition in which tinnitus sufferers experienced their tinnitus with that observed during a brief period of tinnitus suppression (RI) induced by exposure to an appropriate masking sound. Control subjects without tinnitus, matched as closely as possible in age and audiometric function to the tinnitus subjects, were also tested to determine whether the neural changes observed after masking were unique to individuals experiencing tinnitus. Brain activity was probed in tinnitus and in RI by recording the brain response evoked by a 40-Hz amplitude-modulated (AM) sound using either a carrier frequency of 5 kHz (in the TFR of the tinnitus subjects) or 500 Hz (well below this region) with 128-channel electroencephalography (EEG). We extracted from the EEG the 40-Hz auditory steady-state response (ASSR) known to localize to neural sources in A1 (Godey et al., 2001; Bidet-Caulet et al.,. 2007) and the transient N1 response known to localize to distributed sources in the region of the auditory parabelt (called here nonprimary auditory cortex, A2). ASSR sources show a coarse but consistent low-frequency anterolateral, high-frequency posteromedial tonotopic organization (Pantev et al., 1996; Wienbruch et al., 2006; Gander et al., 2010a) that reflects the summation of extracellular field potentials across two cochleotopic maps with strong low-frequency anterolateral and high-frequency posteromedial activations in Heschl's gyrus (Langers et al., 2012). In contrast, N1 sources localize to distributed and cytoarchitectonically heterogeneous regions of A2 (Godey et al., 2001) where tonotopy is lacking or not strongly expressed (Schreiner and Cynader, 1984; Langers et al., 2007; Lütkenhöner et al., 2003). N1 sources appear to integrate sound information over a wide frequency range to form auditory objects and link these objects with inputs from other brain regions in support of adaptive behaviour.

In the present study, these differing properties of ASSR and N1 responses were used to evaluate whether aberrant neural activity occurring specifically in the TFR of A1 underlies the tinnitus percept, as proposed by neural synchrony models of tinnitus (Eggermont and Roberts, 2004; Roberts et al., 2013). If ASSRs are modulated by the presence of neural changes in A1 related to tinnitus, these models predict that differences in the ASSR between tinnitus and control groups under baseline conditions should depend on whether the carrier frequency of the probe stimulus is in the TFR (5 kHz) or below it (500 Hz). Furthermore, changes observed in ASSR responses evoked by 5 kHz probes after forward masking should relate to RI depth and duration in the tinnitus subjects. These results are not expected for N1 owing to the different functional organization of N1 sources outside of the auditory core region. In the following we report experimental findings relating to these hypotheses. Within the limits of our test,