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Research paper

# Psychophysical and neural correlates of noised-induced tinnitus in animals: Intra- and inter-auditory and non-auditory brain structure studies

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ABSTRACT

Tinnitus, a ringing in the ear or head without an external sound source, is a prevalent health problem. It is often associated with a number of limbic-associated disorders such as anxiety, sleep disturbance, and emotional distress. Thus, to investigate tinnitus, it is important to consider both auditory and non-auditory brain structures. This paper summarizes the psychophysical, immunocytochemical and electrophysiological evidence found in rats or hamsters with behavioral evidence of tinnitus. Behaviorally, we tested for tinnitus using a conditioned suppression/avoidance paradigm, gap detection acoustic reflex behavioral paradigm, and our newly developed conditioned licking suppression paradigm. Our new tinnitus behavioral paradigm requires relatively short baseline training, examines frequency specification of tinnitus perception, and achieves sensitive tinnitus testing at an individual level. To test for tinnitus-related anxiety and cognitive impairment, we used the elevated plus maze and Morris water maze. Our results showed that not all animals with tinnitus demonstrate anxiety and cognitive impairment. Immunocytochemically, we found that animals with tinnitus manifested increased Fos-like immunoreactivity (FLI) in both auditory and non-auditory structures. The manner in which FLI appeared suggests that lower brainstem structures may be involved in acute tinnitus whereas the midbrain and cortex are involved in more chronic tinnitus. Meanwhile, animals with tinnitus also manifested increased FLI in non-auditory brain structures that are involved in autonomic reactions, stress, arousal and attention. Electrophysiologically, we found that rats with tinnitus developed increased spontaneous firing in the auditory cortex (AC) and amygdala (AMG), as well as intra- and inter-AC and AMG neurosynchrony, which demonstrate that tinnitus may be actively produced and maintained by the interactions between the AC and AMG.



## 1. Introduction

Tinnitus is a prevalent health condition that affects 10–15% of the adult population (Axelsson and Ringdahl, 1989) and 33% of the elderly population (Nondahl et al., 2002, 2007). In addition, 3–4 million veterans suffer from tinnitus, with up to 1 million in the US seeking clinical services (Cave et al., 2007; Elder and Cristian, 2009). If left untreated, tinnitus may have debilitating consequences and can impact daily life by causing anxiety, irritability, disturbed sleep patterns, and depression (Crocetti et al., 2009; Hasson et al., 2011; Hebert and Lupien, 2007; Hesser et al., 2009; Rossiter et al., 2006; Stevens et al., 2007). Economically, tinnitus has become a top service-connected disability that affects military personnel and veterans, leading to approximately $2 billion in annual disability compensation in the US (VBA, 2013). Therefore, there is an urgent need to find reliable therapies to treat and cure this condition. However, due to limited understanding of the underlying mechanisms of tinnitus, the development of effective treatment strategies have been hindered. Over the last 15 years, numerous animal and clinical studies have yielded a wealth of

*Abbreviations:* AC, auditory cortex; AMG, amygdala; FLI, Fos-like immunoreactivity

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information towards the understanding of tinnitus.

Mechanistically, there is a consensus that tinnitus can be of peripheral or central origin. This view is largely based on clinical studies where the auditory nerve has been resected or a microvascular decompression has been performed at the auditory nerve. These studies demonstrated that roughly 50% of tinnitus patients who undergo these resections continue to experience tinnitus, with some patients experiencing tinnitus exacerbation (House and Brackman, 1981; Moller et al., 1993). For tinnitus of central origin, many lines of evidence indicate that tinnitus arises from central maladaptive plasticity. This plasticity is triggered by peripheral damage, such as through noise exposures (including high-pressure blast shockwaves), salicylate, quinine and cisplatin, which can result in deafferentation and lead to compensatory enhancement of neural activity in the central auditory system (Kaltenbach, 2011; Mao et al., 2012; Roberts et al., 2010). Since noise exposure is the most common inducer of tinnitus, predominant efforts have been directed at investigating noise trauma-induced tinnitus and elucidating the underlying mechanisms. Based on published information, noise trauma may cause hyperactivity (increased spontaneous firing), increased bursting events, hypersynchrony (increased neural synchrony), and tonotopic map reorganization along the auditory pathways. The studied auditory brain structures include the dorsal cochlear nucleus, ventral cochlear nucleus (Kraus et al., 2011; Vogler et al., 2011), inferior colliculus and auditory cortex (AC) (Bauer et al., 2008; Eggermont and Roberts, 2004; Kaltenbach, 2011; Mulders and Robertson, 2011; Zhang et al., 2006).

As described above, tinnitus is frequently accompanied by anxiety, irritability, disturbed sleep patterns, and depression, illustrating the involvement of limbic-associated dysfunctions in the etiology of tinnitus. Thus, in addition to the contribution of neural activity changes in auditory structures, neural activity changes in limbic structures may play an important role in tinnitus. This is not surprising given the direct and indirect connections between the central auditory system and limbic structures (Kraus and Canlon, 2012), as well as the fact that limbic-associated functioning, including cognition and emotion, are frequently compromised in tinnitus sufferers (Hallam et al., 2004; Hebert et al., 2012a; Lewis, 2002; Oishi et al., 2010). Some regard the limbic system as obligatory machinery necessary for tinnitus perception, whereas others consider it an auxiliary neural substrate that is involved in the cognitive and emotional impairments in tinnitus (Hallam et al., 2004; Hallberg and Erlandsson, 1993; Lewis, 2002; Oishi et al., 2010). For example, Jastreboff's model proposes that tinnitus originates in the auditory pathway and involves the limbic system where memories of the phantom sound encoded by the amygdala (AMG) are linked to fear and negative emotions stored in the hippocampus. Nevertheless, it is unclear how the AMG directly contributes to the etiology of tinnitus, how its interactions with auditory structures contribute to the development of tinnitus, and whether other non-auditory brain structures are involved in the etiology of tinnitus.

This paper reviews recent findings from the projects supported by the Tinnitus Research Consortium by focusing on psychophysical correlates of tinnitus, auditory and non-auditory neural correlates of tinnitus, as well as the neurophysiological interactions between auditory and non-auditory centers. Psychophysically, we have, over the years, adopted conditioned suppression/avoidance (Heffner and Harrington, 2002) and unconditioned (gap detection acoustic startle reflex paradigm, Turner et al., 2006) paradigms. Our lab has recently developed a conditioned-licking suppression paradigm that requires relatively short baseline training, possesses tinnitus frequency-specific and loudness-sensitive testing at the individual level, as well as versatility for testing tinnitus that results from different inducers (Pace et al., 2015). In addition to testing for tinnitus, we also tested animals' limbic dysfunctions by measuring anxiety and cognitive impairment. Immunocytochemically, we measured Fos-like immunoreactivity (FLI) in both auditory and non-auditory brain structures of rats with behavioral evidence of tinnitus. Electrophysiologically, we measured neural activity changes in the AC and AMG of rats with noise-induced tinnitus.

## 2. Psychophysical correlates of tinnitus and its associated limbic dysfunctions

### 2.1. Testing behavioral evidence of tinnitus

Although tinnitus can be induced by many factors, it may only manifest in certain individuals or time points (Cave et al., 2007; Griest and Bishop, 1998). Consequently, numerous behavioral paradigms have been established to determine the perception and characteristics of tinnitus in animals (Bauer and Brozoski, 2001; Berger et al., 2013; Guitton and Dudai, 2007; Heffner, 2011; Heffner and Harrington, 2002; Jastreboff et al., 1988; Kizawa et al., 2010; Lobarinas et al., 2004; Longenecker and Galazyuk, 2012; Luo et al., 2014; Norman et al., 2012; Pace and Zhang, 2013; Ruttiger et al., 2003; Sederholm and Swedberg, 2013; Stolzberg et al., 2013; Turner et al., 2006; Yang et al., 2011; Zheng et al., 2011c). Over the past 15 years, our lab has adopted several paradigms, including conditioned suppression/avoidance (Heffner and Harrington, 2002; Zhang et al., 2003b), gap-detection (Luo et al., 2012; Pace and Zhang, 2013; Zhang et al., 2011), and a recently developed conditioned licking suppression paradigm (Pace et al., 2015).

For the conditioned suppression/avoidance paradigm, water-deprived hamsters were trained to drink water from a spout during the presentation of broadband noise and/or tones (Heffner and Harrington, 2002). Attempts to drink water during silence were suppressed by punishment with a mild electrical shock. Following intense tone exposure, shocks were removed and hamsters that spent a lower average percentage of time drinking during sound trials and not drinking during silent trials were considered tinnitus positive. Hamsters were tested for at least 5–10 days following tone exposure. Key advantages for this early behavioral model were that sufficient data could be collected in a single testing session, and that individual animals could be assessed for tinnitus. The drawbacks, however, were that animals required 32–35 testing sessions to reach baseline criteria and they could not be tested for long-lasting tinnitus.

As an alternative to operant conditioning models, gap-detection has evolved over the past decade into a widely used tool for tinnitus assessment in rodents. The strengths of the gap-detection test are that food/water-deprivation and shock punishments can be avoided, enabling shorter training periods. Additionally, the frequency range of tinnitus can be determined. In our studies using gap-detection, we have found evidence of acute and lasting noise-type and tonal-type tinnitus following noise exposure (Luo et al., 2012; Pace and Zhang, 2013; Zhang et al., 2011). We were also able to identify tinnitus manifestation and frequencies in individual rats, as detailed in our recent report (Pace and Zhang, 2013) (Fig. 1). In addition, we have demonstrated suppression of behavioral evidence of tinnitus using electrical stimulation of the auditory cortex (Zhang et al., 2011) and dorsal cochlear nucleus (Luo et al., 2012). While these findings are collectively in line with the literature (Bauer et al., 2008; Brozoski et al., 2002; De Ridder et al., 2006a; Seidman et al., 2008; Zhang and Kaltenbach, 1998), it is important that multiple behavioral models of tinnitus are used to validate results, especially since tinnitus may not always impair certain measurements like gap-detection (Campolo et al., 2013).

Recently, we have developed a tinnitus paradigm that utilizes conditioned licking suppression (Pace et al., 2015). The benefits of

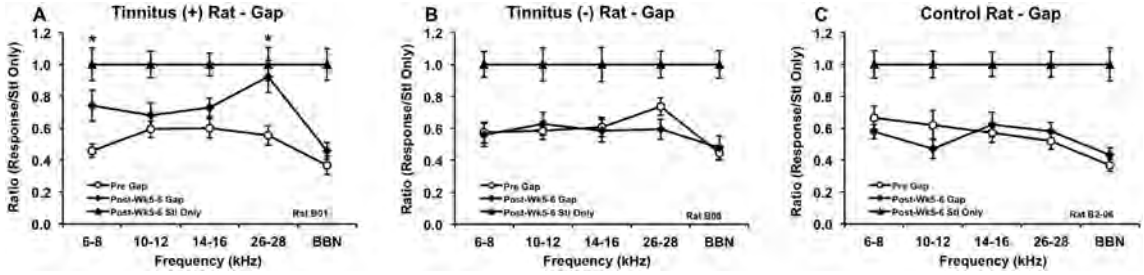


**Fig. 1.** Gap and startle only ratios from a representative tinnitus$^{(+)}$, tinnitus$^{(-)}$, and control rat. In the tinnitus$^{(+)}$ rat (A), 5–6 weeks post-exposure GAP ratios were significantly higher than pre-exposure ratios but not significantly lower than startle only ratios, indicating tinnitus at 6–8 and 26–28 kHz. Neither the tinnitus$^{(-)}$ (B) nor the control rat (C) exhibited tinnitus. Error bars represent the standard error of the mean (SEM). * indicates significance $P < 0.05$. Adapted from Pace and Zhang (2013).

this paradigm are that rats can reach stable baseline performance in only 10 to 16 testing sessions, the frequency range of tinnitus can be determined, and tinnitus can be assessed in individual rats. To accomplish this, water-deprived rats were trained to lick a horizontal spout during narrowband sound trials in order to receive water rewards. They were punished with a mild, 50% reinforced foot shock (0.25–0.75 mA) when they licked the spout during silent trials, and thus learned to minimize silent trial licks. Consequently, rats were considered tinnitus positive if they increased silent trial licking relative to baseline performance. Increased silent trial licks following specific frequency bands of sound trials would also indicate the tinnitus frequency range. After noise-exposure (8–16 kHz, 105–110 dB, 2hr), we found that about 50% rats exhibited lasting tinnitus through 7 weeks post-exposure, as suggested by an increased number of silent trial licks (Fig. 2A–B). Importantly, neither tinnitus positive nor tinnitus negative rats showed permanent hearing loss or changes in sound trial licks (Fig. 2C–D), indicating that overall sound sensitivity and responsivity remained consistent. Thus, our paradigm provides a relatively fast and robust method for screening tinnitus behavior in rats, which is vital for mechanistic studies as well as therapeutic drug and prostheses development.

### 2.2. Testing of limbic dysfunctions

Individuals with tinnitus can experience difficulties including problems concentrating, sleeping, irritability, increased risk for mood and anxiety disorders, and even suicide (Hebert et al., 2012b; Lewis, 2002; Lewis et al., 1994; Oishi et al., 2010). These dysfunctions can be related to the limbic system, and indeed, tinnitus patients have often shown altered activity and structure in limbic regions such as the amygdala and hippocampus (Landgrebe et al., 2009; Lockwood et al., 1998; Schmidt et al., 2013). Given the complexity and variability between tinnitus perception and limbic-associated functioning (Andersson et al., 2009; Crocetti et al., 2009; Hesser et al., 2009; Oishi et al., 2010; Rossiter et al., 2006; Stevens

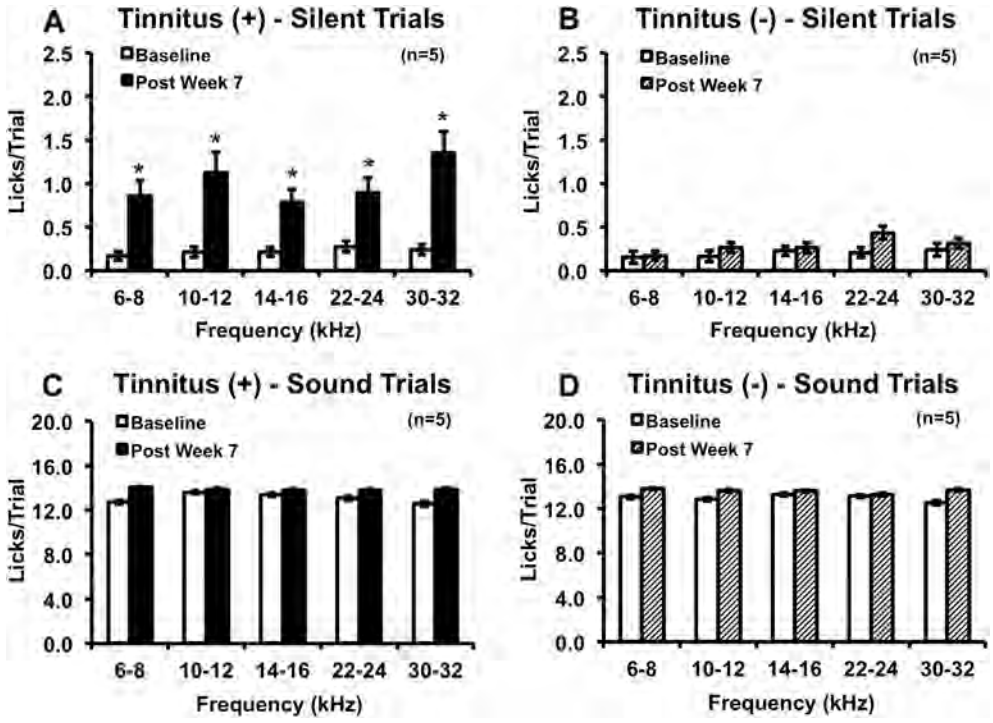


**Fig. 2.** Operant conditioning behavioral paradigm for testing noise-induced tinnitus. At 7 weeks following noise exposure, tinnitus$^{(+)}$ rats displayed a significant increase in silent trial spout licking across all-frequency bands (A), suggesting tinnitus. Tinnitus$^{(-)}$ rats, on the other hand, displayed no changes in post-exposure silent trial licking (B). Neither group exhibited changes in sound trial licking (C–D), indicating that overall activity levels remained consistent and were unlikely to be affected by changes in sound sensitivity, like hearing loss. Error bars represent standard error of the mean. * indicates significant increase.

et al., 2007), animal models play a critical role in elucidating their interrelationships. The main challenge is finding methods to identify cognitive-emotional dysfunction in animals and properly extrapolating that dysfunction to humans.

After rats underwent noise exposure, we have assessed their behavior on the elevated plus maze and Morris water maze, respectively, to determine whether tinnitus positive rats displayed greater impairment (Pace and Zhang, 2013). For the plus maze test, animals with high anxiety levels commit less entries and time in the exposed, open arms of the maze and instead gravitate towards the safer, enclosed arms. Following tone exposure, we found no significant increase in anxiety for tinnitus positive or negative groups as a whole (Pace and Zhang, 2013). However, when assessing individual rats, we observed that the majority of rats with the highest anxiety levels also had tinnitus. This matches clinical studies where only certain tinnitus subjects have significant anxiety (Crocetti et al., 2009; Hesser et al., 2009; Oishi et al., 2010) (Belli et al., 2008; Zoger et al., 2001, 2006) An earlier animal study also found no significant increase in anxiety for noise-exposed tinnitus positive rats (Zheng et al., 2011b) although rats were not individually assessed for anxiety or tinnitus. Further assessment of these and additional behaviors such as grooming microstructure, sucrose consumption, weight, and other measurements may help clarify tinnitus-related emotional distress in animals.

In the Morris water maze test, animals swim through a water tank and use spatial cues to locate a hidden, underwater platform. Animals that take longer to find the platform and spend less time in the platform area are considered to have impaired spatial learning and memory. After we subjected rats to noise exposure, however, we found no spatial cognitive deficits in tinnitus positive or negative rats (Pace and Zhang, 2013). These results were supported by previous studies where no spatial cognitive impairment was found in rats with noise-induced tinnitus (Zheng et al., 2011a). Conversely, rats with noise-induced tinnitus have shown altered impulse control and social interaction (Zheng et al., 2011b, 2011c). This appears to reflect the clinical situation, where only certain tests have found cognitive dysfunction in a portion of tinnitus subjects (Andersson et al., 2009; Hallam et al., 2004; Rossiter et al., 2006; Stevens et al., 2007) Like assessments for tinnitus-related emotional distress, more work is clearly required to elucidate limbic-associated cognitive functioning. Given the wide range of dysfunction, research on both fronts is urgently needed.

## 3. Neural correlates of noise-induced tinnitus in auditory structures

### 3.1. Increased FLI in auditory brain structures of hamsters with tinnitus

*C-fos* immunocytochemistry is used to map functional activity changes along the auditory pathways with cellular resolution. This method is based on the fact that the immediate early proto-oncogene *c-fos* responds to a variety of external stimuli and serves as functional marker (Alagramam et al., 2014; Lu et al., 2014; Ogata et al., 2015). The usage of this method was prompted by human studies using PET and functional MRI showing that some types of tinnitus are associated with increased metabolic activity at both cortical and subcortical levels of the auditory system (Lockwood et al., 1998; Melcher et al., 2009; Boyen et al., 2014; Gu et al., 2010). In addition, [$^{14}$C]-2-deoxyglucose autoradiography (2-DG) was also used to detect the neural correlates of tinnitus (Paul et al., 2009; Schecklmann et al., 2013; Zhang et al., 2003a). Compared to single- or multi-unit electrophysiology, PET, fMRI, 2-DG and *c-fos* immunocytochemistry allow measurement of neural activity or information to reveal neural activity changes in multiple brain regions. Only the latter (i.e., *c-fos* immunocytochemistry) achieves cellular resolution. Experiments in gerbils have demonstrated increased c-fos expression in the AC and numerous non-auditory brain structures after treatment with sodium salicylate, which was assumed to induce tinnitus (Wallhäuser-Franke et al., 2003). The increases in *c-fos* expression have also been observed in some auditory and non-auditory areas of animals within a few hours following exposure to impulse noise (Wallhäuser-Franke et al., 2003). However, the long-term effects of sound exposure on Fos-like immunoreactivity (FLI) in the brain and the relationship of these effects with tinnitus have yet to be reported. Furthermore, studies using the above methods have not been conducted in animal subjects that had been exposed to intense sound and tested behaviorally for tinnitus.

Prior to *c-fos* immunocytochemistry, we first evaluated behavioral evidence of noise-induced tinnitus as previously reported (Heffner and Harrington, 2002) and described above (see Section 2.1). The performance score was calculated as the mean percentage time that a hamster was in contact with a waterspout during sound trials and was not in contact with a waterspout during silence. Thus hamsters with tinnitus would expectedly score lower than hamsters without tinnitus, since hamsters would hear tinnitus during silent trials and be less likely stop drinking on trials (Heffner and Harrington, 2002). Following baseline testing, the hamster was exposed to a 10 kHz tone at 125–129 dB SPL for 4 h. Post-exposure behavioral testing was performed to examine the presence of tinnitus. Our results showed that the scores of exposed hamsters averaged 62.29 and ranged from 54.31 to 69.18, significantly lower than the unexposed group, which averaged 72.63 and ranged from 60.90 to 77.14 (Zhang et al., 2003). The lower mean scores of exposed hamsters suggests that these hamsters tended to maintain waterspout contact during silent trials as though they heard a sound, even though no external sound was present, this indicates tinnitus. Following tinnitus verification, the hamsters were euthanized with a lethal dose of anesthetic. Their brains were removed and processed immunocytochemically (Zhang et al., 2003). The density of FLI was bilaterally quantified on both auditory and non-auditory brain structures (Zhang et al., 2003).

The results showed that, compared to naïve controls, hamsters that demonstrated evidence of tinnitus manifested significant increases of FLI in the contralateral lateral lemniscus, and bilateral central nucleus of the inferior colliculus and AC (Figs. 3 and 4). Interestingly, we did not observe increased FLI in the cochlear nucleus, lateral superior olive, nucleus of trapezoid body, and ventral subdivision of the medial geniculate body (Zhang et al., 2003). The increases in the auditory structures may result from increased spontaneous firing, as increased FLI in neural systems represents increased major activity (Morgan and Curran, 1991). Indeed, tinnitus inducers such as noise exposure are known to cause increased spontaneous firing in the inferior colliculus (Bauer et al., 2008) and AC (Llano et al., 2012; Norena and Eggermont, 2003). The main discrepancy is the reduced FLI activity in the cochlear nucleus even though it has been reported that noise exposure causes increased spontaneous firing in both the dorsal cochlear nucleus (Kaltenbach, 2011; Roberts et al., 2010) and ventral cochlear nucleus (Kraus et al., 2011; Vogler et al., 2011). This calls into question the activity-dependent mechanism of increased FLI in other auditory structures. One possible explanation of this result may be that noise-induced increased spontaneous firing in the cochlear nucleus was less potent compared to the increased neural activity in other auditory brain structures. Additionally, acoustic trauma is known to be a major trigger of plastic alterations in the central auditory system, and the capacity for some forms of plasticity is greater at midbrain and cortical levels than at lower levels of the system (Zhang et al., 2003). For example, hearing loss-induced

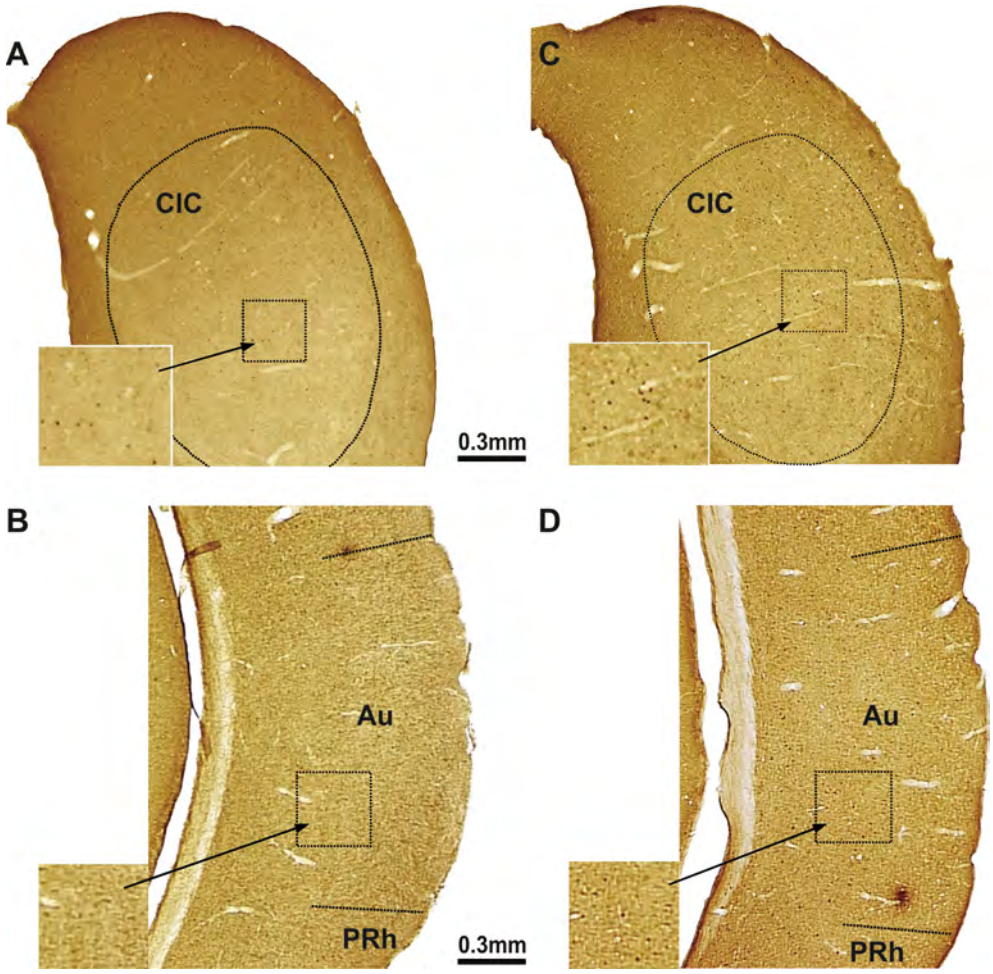


**Fig. 3.** Photomicrographs showing FLI in the CIC and AC of both unexposed (A, B) and exposed (C, D) animals. The magnified details of Fos labeling in the CIC and Au are shown in the insets for both groups. Au – primary auditory cortex; CIC – central nucleus of the inferior colliculus; PRh – perirhinal cortex. Adapted from Zhang et al. (2003b).

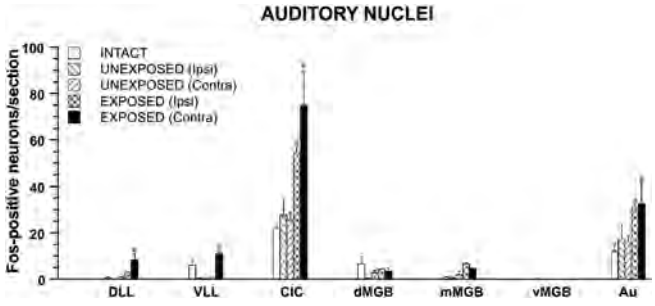


**Fig. 4.** Quantified FLI in auditory structures of intact, unexposed and exposed animals. (I) – ipsilateral; (C) – contralateral side, with respect to the exposed left ears. Comparison of FLI between exposed and unexposed animals for each structure was made on the same side of the brain. DLL, VLL – dorsal and ventral nucleus of lateral lemniscus; CIC – central nucleus of the inferior colliculus; dMGB, mMGB, vMGB – dorsal, medial and ventral subdivision of medial geniculate body; Au – primary auditory cortex. Value $p < 0.05$(*). Adapted from Zhang et al. (2003b).

reorganizations of the tonotopic map have been found at the midbrain and cortical levels (Robertson and Irvine 1989; Snyder et al., 2000), but the cochlear nucleus appears to show little or no capacity for this type of plasticity (Willott et al., 1991; Kaltenbach et al., 1992). Furthermore, it is possible that lower brainstem structures such as the dorsal cochlear nucleus are involved in acute tinnitus whereas the midbrain and cortex are involved in more chronic tinnitus.

### 3.2. Increased spontaneous firing in the AC of rats with tinnitus

As described above, increased spontaneous firing has been demonstrated in a number of auditory structures including the dorsal and ventral cochlear nucleus, inferior colliculus, and AC following administration of noise exposure, salicylate or quinine (Britvina and Eggermont, 2008; Engineer et al., 2011; Munguia et al., 2013; Norena and Eggermont, 2006).

Simultaneous electrophysiological recordings were conducted with microelectrode arrays chronically implanted in multiple structures in the AC and AMG of three rat groups, The three rat groups consisted of a Tinnitus(+) group in which rats developed tinnitus after noise exposure, a Tinnitus(−) group in which rats did not develop tinnitus, and a Control group in which rats were not noise-exposed and did not develop tinnitus. Aseptic surgery was performed to implant electrode arrays in the right AC and AMG for chronic recordings, targeting the primary AC and the basolateral region of the amygdala, respectively. Recordings were conducted on a weekly basis ~10 days after recovery from surgery. Spontaneous and nonspontaneous (i.e. evoked) activity was recorded under isofluorane anesthesia. For each recording session, spontaneous single- and multi-unit activity was recorded for 10 min at 30-min intervals before and after tone exposure. Spontaneous firing

rate was then calculated by dividing the activity by time used for recording. Nonspontaneous activity was recorded during frequency tuning curves in the AC were acquired before and after tone exposure to determine tonotopic representations of spontaneous and stimulus-driven activity and plastic reorganization. Along with histology results, all recording electrodes were identified for tonotopic representation during data analysis.

As shown in Fig. 5, there was a significant increase in spontaneous firing rate in the AC of Tinnitus(+) rats compared to both controls and Tinnitus(−) rats. Such increased spontaneous firing occurred at both 2 and 6 weeks after noise exposure. At the same time, we did not observe any significant difference in spontaneous firing between controls and Tinnitus(−) rats. This indicates that the hyperactivity found in the AC of Tinnitus(+) rats directly represents the neural substrate underlying tinnitus. The results suggested that the tinnitus percepts are of cortical origin.

### 3.3. Increased spontaneous neurosynchrony in the AC of rats with tinnitus

Neural synchrony reflects the degree of firing of different neural components in a time domain. Eggermont (Eggermont and Tass, 2015) recently divided neural synchrony into three types, including 1) microsynchrony, referring to nearly simultaneous firing of individual neurons; 2) mesosynchrony, referring to synchronized membrane-potential changes in local neural groups as reflected in the local field potentials; and 3) macrosynchrony, referring to oscillatory brain waves in the EEG signals. In this paper, we include microsynchrony data recorded from the AC and AMG to address the interactions between the AC and AMG. Neurosynchrony was calculated based on the peak value per 5 ms for each frequency band and location. We grouped the electrodes by frequency bands based on the characteristic frequencies recorded from tuning curves. The matrix of pair wise peak correlation values from within- and in-between the AC and AMG was subjected to a hierarchical clustering procedure and analyzed by a custom made program in MatLab and NeuroExplorer. The peak cross-correlation coefficients (C) were obtained from the equation of $C = S_{xy}/\sqrt{S_x S_y}$, where $S_x$ and $S_y$ are the number of spikes in channel x and channel y. The grouped neurosynchrony data at three frequency loci were then analyzed for significance using repeated measures ANOVA followed by post-hoc t-test to compare for differences between the noise trauma and control rats, or the tinnitus(+) and tinnitus(−) rats after noise exposure. Neurosynchronization index values were analyzed using IBM SPSS Statistics version 21.0. One-way ANOVA was performed with post hoc Bonderroni multiple comparisons to compare the synchrony index values among the auditory structures. A $p < 0.05$ was considered statistically significant for the data analyses.

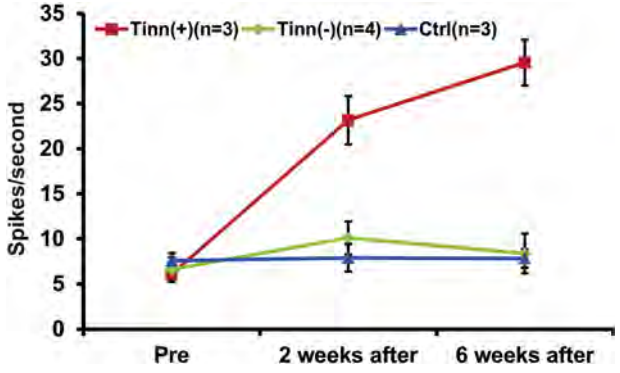


**Fig. 5.** A. Changes in spontaneous firing rates (SFRs) in the auditory cortex (AC) over time in rats under anesthesia. The neural hyperactivity became robust in the tinnitus(+) group compared to tinnitus(−) and control groups.

Our data showed that neural synchrony, as represented by the correlogram ratio, was increased in the AC of both tinnitus(+) and tinnitus(−) rats at 2 weeks after noise trauma (Fig. 6). Such increased neurosynchrony persisted in the AC of tinnitus(+) rats at six weeks after noise trauma. However, the synchrony in the AC of tinnitus(−) rats returned to control-level values. Our data showing the general increase of synchrony in the AC after noise exposure is consistent with the earlier studies (Engineer et al., 2011; Komiya and Eggermont, 2000). For example, increased inter-neuronal synchrony within the reorganized part of the cortex was found at 7–16 weeks after exposure in cats (Komiya and Eggermont, 2000). While those cats were diagnosed with hearing loss, it was unknown whether they perceived tinnitus. Eggermont and his research team also reported, however, that an increased synchrony in the AC can occur immediately following noise exposure or quinine treatment (Norena and Eggermont, 2003, 2005; Ochi and Eggermont, 1997). In addition, and similar to our study, multiunit recording was conducted in the AC of rats with noise-induced tinnitus behavior, which demonstrated increased synchrony (Engineer et al., 2011). Moreover, both groups have found that synchronized activity is related to cortical reorganization or frequency tuning in the AC after noise exposure. Taken together, these studies and ours suggest that correlation between cortical reorganization and inter-neural synchrony may be related to tinnitus induced by acoustic trauma. Thus, both enhanced synchronization and frequency tuning changes in the AC may be directly responsible for tinnitus (Bauer et al., 2008; Eggermont and Roberts, 2004). Future study can be focused on the pattern of frequency tuning or neuroplastic response in the AC of noise-induced tinnitus(+) rats.

## 4. Neural correlates of noise-induced tinnitus in non-auditory structures

### 4.1. Increased FLI in non-auditory brain structures of animals with tinnitus

C-fos immunocytochemistry studies showed that hamsters with noise-induced tinnitus manifested significant increases of FLI in a number of non-auditory brain structures, including the bilateral locus coeruleus, lateral parabrachial nucleus, lateral hypothalamic area, posterior hypothalamic area, paraventricular thalamic nucleus, lateral supramammillary nucleus, ventral premammillary nucleus, central amygdaloid nucleus, lateral amygdaloid nucleus, basolateral amygdaloid nucleus, and contralateral arcuate nucleus (Figs. 7 and 8) (Zhang et al., 2003b). When comparing the ipsilateral and contralateral sides of exposed hamsters, no appreciable differences in FLI were observed for the majority of structures. Exceptions were that FLI was higher in the contralateral lateral lemniscus, central nucleus of the inferior colliculus, ipsilateral central amygdaloid nucleus, and contralateral lateral supramammillary nucleus than the opposite side. The increased FLI activity in these non-auditory structures suggests their involvement in the noise-induced tinnitus (Zhang et al., 2003b). Mechanistically, the locus coeruleus, a noradrenergic nucleus, is known to mediate arousal/sleep (Del Cid-Pellitero and Jones, 2012; Koh et al., 2015), stress (Koh et al., 2015), and responses to noxious stimulation (George et al., 2013). The lateral parabrachial nucleus is a major relay center of visceral sensory information to the forebrain. The locus coeruleus, and medullary autonomic regulatory centers, and its neurons are activated by cardiovascular stimuli (Wang et al., 2014). The increased FLI activity in the locus coeruleus and lateral parabrachial nucleus suggests that noise-induced tinnitus may

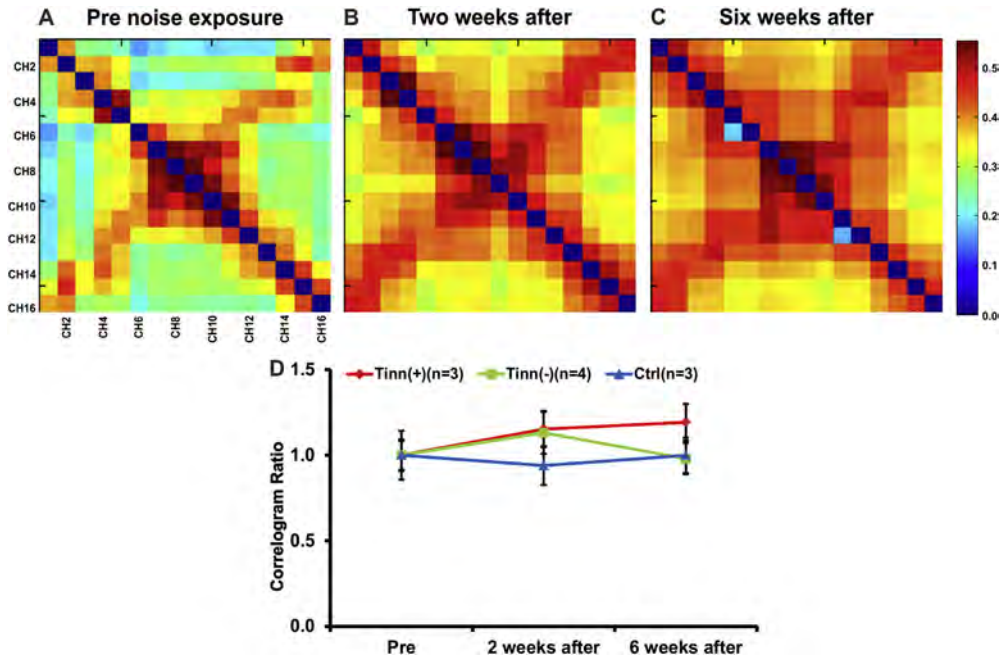


**Fig. 6.** A–C. Neurosynchrony as revealed by correlogram rate matrix in the AC of the tinnitus$^{+}$ group. The matrix provides the visualization and evaluation of neurosynchrony of multi unit recording from different channels. The resultant grid displays the reference channel (y-axis) vs. target channel (x-axis), with the z-axis color proportional to the degree of correlation. The rate of correlation increased significantly after noise trauma. D. Changes in the normalized correlogram rates in the AMG of anesthetized rats. The correlogram ratio of the tinnitus$^{+}$ group increased after noise trauma compared to the tinnitus$^{-}$ and control groups.

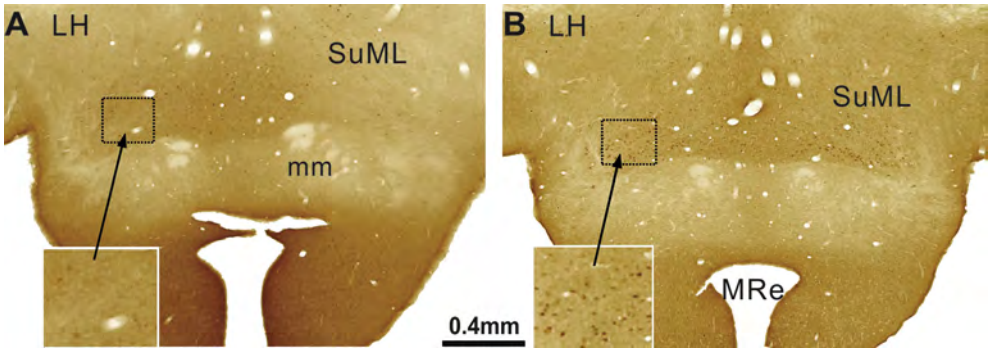


**Fig. 7.** Photomicrographs showing FLI in non-auditory structures of unexposed (A) and exposed (B) animals. The magnified details of Fos labeling in the SuML are shown in the insets for both groups. Au – primary auditory cortex; MRe – mammillary recess of 3rd ventricle; mm – mammillary peduncle. Adapted from Zhang et al. (2003b).

have also increased stress in affected hamsters. The increased FLI activity in the lateral hypothalamic area, posterior hypothalamic area, paraventricular thalamic nucleus, lateral supramammillary nucleus, and ventral premammillary nucleus clearly suggested the involvement of the hypothalamus in the autonomic responses to tinnitus manifestation. This may be because the hypothalamus integrates neuroendocrine, autonomic, and behavioral responses to stress (Bondarenko et al., 2015; Lkhagvasuren et al., 2014; Zheng et al., 2014). Furthermore, the increased FLI activity in the amygdala (AMG) indicates that the noise-induced tinnitus had a significant emotional component. Indeed, the AMG is an emotional gating center and is directly involved in fear-conditioning, memory and the processing of emotional signals (Janak and Tye, 2015; Rolls, 2015). Consistent with the previous notions (Wallhausser-Franke, 1997), intense noise exposure not only causes tinnitus, as indicated by behavioral testing, but is also likely to impact hamsters' arousal, attention and fear-conditioning-related emotion. The results also mirror previous clinical studies in that limbic structures are often activated during tinnitus perception (Carpenter-Thompson et al., 2014). Finally, our study showed that stimulation with moderate-level and high-frequency tones also increased FLI in non-auditory structures. This implicates the involvement of auditory attention, especially sharp and annoying perceptions to high-frequency tones (Zwicker and Fastl, 1990). However, since the current sound exposure induced ABR threshold shifts, the hearing loss-related effects on FLI activity remain to be differentiated from tinnitus-specific effects.

### *4.2. Increased spontaneous firing in the AMG of animals with tinnitus*

Among the above autonomic and limbic structures that showed FLI changes in animals with behavioral evidence of tinnitus, the AMG is thought to be a pivotal structure linking tinnitus to stress, emotion, anxiety, and memory (Cacace, 2004; De Ridder et al., 2006b; Hui et al., 2006). It is connected with auditory structures (Kraus and Canlon, 2012), such as the AC, to mediate auditory fear conditioning (Maren et al., 2001), learning and memory (Poremba

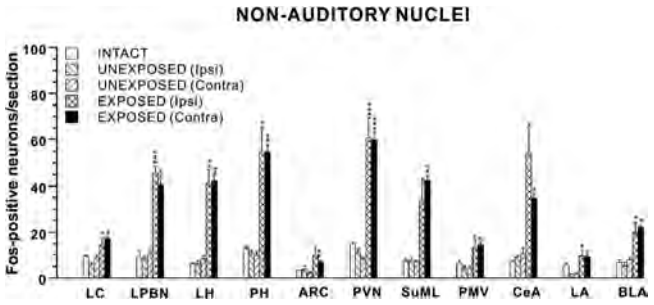


**Fig. 8.** Quantified FLI in non-auditory structures of intact, unexposed and exposed animals. (I) – ipsilateral; (C) – contralateral side, with respect to the exposed left ears. Comparison of FLI between exposed and unexposed animals for each structure was made on the same side of the brain. LC – locus coeruleus; LPBN – lateral parabrachial nucleus; LH – lateral hypothalamic area; PH – posterior hypothalamic area; ARC – arcuate hypothalamic nucleus; PVN – paraventricular thalamic nucleus; SuML – lateral supramammillary nucleus; PMV – ventral premammillary nucleus; CeA – central amygdaloid nucleus; LA – lateral amygdaloid nucleus; BLA – basolateral amygdaloid nucleus; Value $p < 0.05$(*), $p < 0.01$(**) and $p < 0.001$ (***). Adapted from Zhang et al. (2003b).

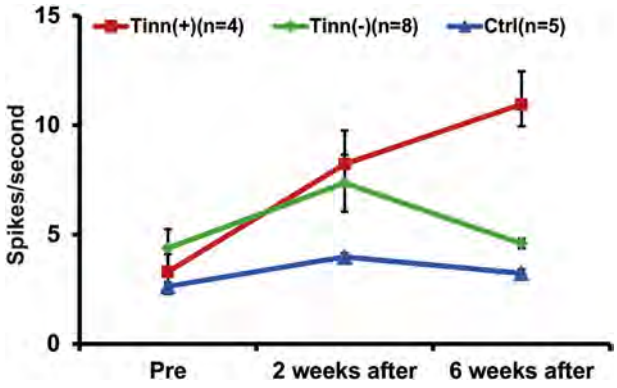


**Fig. 9.** A. Changes in spontaneous firing rates (SFRs) in the amygdala (AMG) over time in rats under anesthesia. The neural hyperactivity became robust in the tinnitus$^{(+)}$ group compared to tinnitus$^{(-)}$ and control groups. The spontaneous firing rate of the tinnitus-negative group increased temporarily then returned to normal level.

and Gabriel, 1997; Roozendaal et al., 2009), and emotional significance of sounds (Ledoux et al., 1990; Wu et al., 2007). The AMG is also involved in body homeostasis (Aggleton, 1993) and integrates inflammation-derived information to coordinate behavioral and autonomic responses, whereas changes in AMG activity are temporally related to an increase in anxiety-like behavior (Engler et al., 2011). Additionally, the AMG responds to environmental disturbances; for example, it is involved in the emotional processing of anxiety (Wu et al., 2007) and memory (Roozendaal et al., 2009), the orchestration of body homeostasis (Aggleton, 1993), sensorimotor gating (Decker et al., 1995), and in mediating post-traumatic stress disorder (White et al., 2015). Taken together, it is highly likely that the AMG is involved in noise-induced tinnitus.

To demonstrate the neurophysiological involvement of the AMG in tinnitus, we chronically implanted multichannel electrode arrays in the basolateral nucleus of the AMG and performed electrophysiological recordings in rats with noise-induced tinnitus. As described previously, rats were behaviorally tested for tinnitus using the gap detection acoustic startle reflex paradigm before and after an intense tone exposure (10 kHz, 105 dB SPL, 3 h duration). The recording was conducted at different time points to monitor the progression of tinnitus-related neural activity under anesthesia. Our results showed that spontaneous firing rate (SFR) in the AMG was significantly higher in rats with noise-induced tinnitus at 6 weeks post-exposure, compared to rats that had been exposed to the same noise but did not develop tinnitus and naïve controls (Fig. 9). In addition, the neurosynchrony in the AMG changed incrementally over time (Fig. 9). Along the same time, Chen and colleagues reported that, following administration with salicylate, neuronal activity in the rat AMG was selectively enhanced in high-frequency regions that match the pitch of salicylate-induced tinnitus (Chen et al., 2012). This is related to findings by Bordi and Le Doux, which indicated that certain amygdala neurons are turned to sound stimulation (Bordi and LeDoux, 1992). Mechanistically, the induced increased spontaneous firing rate in the AMG of rats may result from reduced GABAergic input from the inter-inhibitory neurons onto the principal neurons in the basolateral nucleus of the AMG. Such reduced GABAergic input from the inter-inhibitory neurons might be caused by both excitatory AMPA and NMDA input from both the medial geniculate body and AC (Doyere et al., 2003), which may have been induced by intense noise exposure for tinnitus induction. Thus, it is of importance and interest to know whether the noise-induced AMG activation, which is associated with tinnitus, is caused by altered balance between the mediate geniculate body and AC afferents to the AMG.

### 4.3. *Increased spontaneous neurosynchrony in the AMG of rats with tinnitus*

As described in Section 3.3, microsynchrony data were obtained and calculated in the AMG by examining correlograms to assess how AMG neurons' spontaneous firing was correlated. We found greater neurosynchrony in tinnitus(+) rats than in tinnitus(−) and naïve control rats (Fig. 10D). Such increased neurosynchrony furthered over 2 and 6 weeks, as seen in correlogram plots (see more reddish distributions of synchrony data in panels B and C *versus* panel A of Fig. 10 and the quantified data in Fig. 10D). In addition, there was no significant difference in the neurosynchrony between the tinnitus(−) and control groups. Such results indicate that the enhanced neurosychrony in the AMG represents neural signals underlying the behavioral evidence of tinnitus.

Based on the coordinates from the rat brain atlas and histological verification, the electrode arrays were implanted in the basolateral nucleus of the AMG. The basolateral nucleus of the AMG consists of both principal and GABAergic inter-inhibitory neurons. As described above, if the input from the inter-inhibitory neurons is reduced by excessive excitatory input from both the medial geniculate body and AC (Doyere et al., 2003), intuitively the increased neurosynchrony in the AMG possibly represent synchronous firing between the principal neurons in the basolateral nucleus of the AMG. Such enhanced neurosynchrony in the AMG suggests that the limbic involvement of tinnitus is closely related to active interactions between the principal neurons in the AMG.

## 5. Interactive neural correlates of noise-induced tinnitus in auditory and non-auditory structures

The amygdala (AMG) is one important limbic structure that has been thought to be linked to bothersome tinnitus (Carpenter-Thompson et al., 2014; Chen et al., 2012; Jastreboff, 2004; Shulman et al., 2009; Wallhausser-Franke et al., 2006; Zhang et al., 2008, 2003b) through its role in emotional processing of anxiety, memory (Chavez et al., 2009; Sigurdsson et al., 2007) and sensorimotor gating (Decker et al., 1995). Anatomically, the AMG sends direct projections to many brain regions (Price, 2003), among which it forms circuits with auditory structures, such as the AC, to mediate auditory fear conditioning (Maren et al., 2001), learning and memory (Poremba and Gabriel, 1997), and to initiate

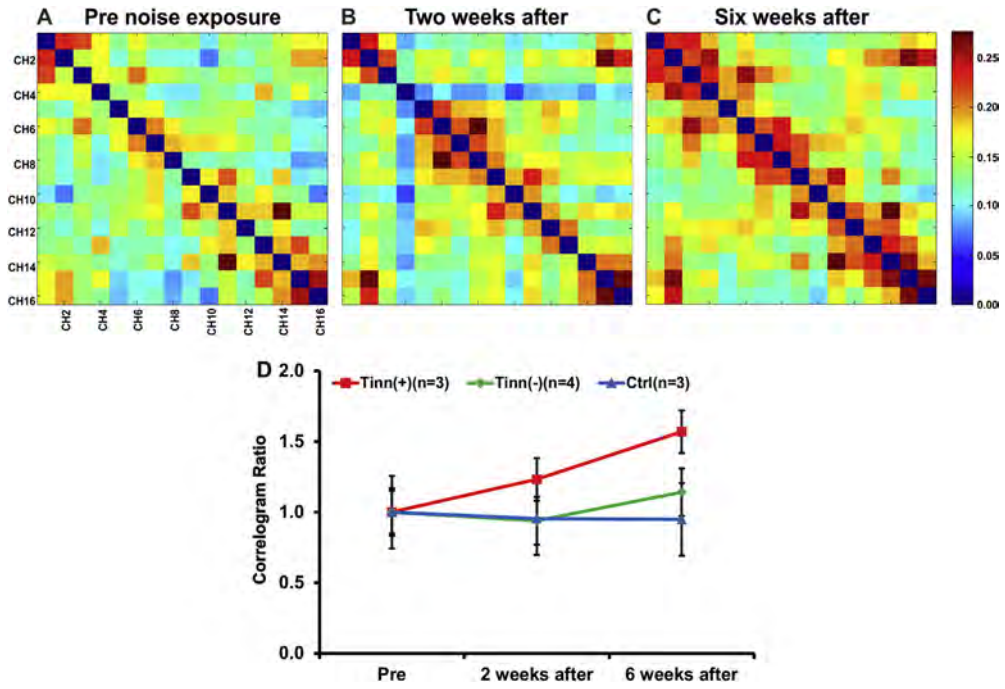


**Fig. 10.** A–C. Neurosynchrony as revealed by correlogram rate matrix in the AMG of the tinnitus$^{(+)}$ group. The matrix provides the visualization and evaluation of neurosynchrony of multi unit recording from different channels. The resultant grid displays the reference channel (y-axis) vs. target channel (x-axis), with the z-axis color proportional to the degree of correlation. The rate of correlation increased significantly after noise trauma. D. Changes in the normalized correlogram rates in the AMG of anesthetized rats. The correlogram ratio of the tinnitus$^{+}$ group increased significantly after noise trauma compared to the tinnitus$^{(-)}$ and control groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

processing of emotionally significant stimuli (Ledoux et al., 1990). The auditory thalamus and AC project to the AMG (Pan et al., 2009; Winer, 2006). This linkage may contribute to establishment of conditioned reactions to fear, involving a cascade of reactions related to the AMG (Huang et al., 2005; Poremba and Gabriel, 1997; Sah et al., 2003). The output of the AMG affects information processing and plasticity in the AC (Duvel et al., 2001) which is mediated by direct amygdaloauditory cortical projections (Duvel et al., 2001) and indirect projections through the cholinergic basal forebrain or hippocampal formation (Pitkanen et al., 2000).

To determine whether AC-AMG temporal coupling is involved in the etiology of noise-induced tinnitus, we performed simultaneous electrophysiological recordings of single- and multi-unit activity in both the AC and AMG. As described in Section 3.3, microsynchrony was calculated based on the peak value per 5 ms for each pair of recording sites from both the AC and AMG. Fig. 11 showed that the correlogram ratio values of the tinnitus positive group significantly increased compared to tinnitus negative and control groups. Interestingly such increase did not manifest in a uniform pattern. Before noise exposure to induce tinnitus, a moderate level of synchrony was found between the AC and AMG, but mainly between the rostral and caudal portion of the AMG and the entire AC (Fig. 11A). At 2 and 6 weeks after noise exposure, the increased synchrony predominantly occurred between the high-frequency regions of the AC and the entire AMG (Fig. 11B–C).

The current results are consistent with a previous report that neural activity in the AC positively co-varies with that in the AMG (Morris et al., 1998). In addition, the output of the AMG affects information processing and plasticity in the AC (Armony et al., 1998; Duvel et al., 2001) which is mediated by direct amygdaloauditory cortical projections (McDonald and Jackson, 1987; Yukie, 2002). After noise exposure to induce tinnitus, the increased neurosynchrony between the AMG and AC may underlie both the sound perception through the auditory pathways and emotional distress through the limbic system. This is also supported by the notion that increased interneuron synchrony generally yields a more efficient excitation of downstream neurons (Eggermont and Tass, 2015), i.e., in both the AMG and AC. We did not see increased neurosynchrony in tinnitus(−) rats, potentially due to less significant loss of afferent input to the high-frequency region of the AC in those rats, compared to tinnitus(+). Second, in the tinnitus(+) rats, the more susceptible high-frequency region in the AC lost normal afferent input, which triggers maladaptive plasticity by gain up-regulation to maintain homeostasis. Such gain upregulation may result in enhanced auditory input to the high-frequency region in the AC from adjacent or lower-frequency regions from the AC or subcortical nuclei. In the AMG, there is a possibility that noise-trauma-induced excitotoxicity through AC afferent input onto the inter-inhibitory neurons in the AMG may have diminished the inhibitory effects on the principal neurons in the basolateral nucleus of the AMG. This eventually causes increased firing in the AMG, which in turn leads to the synchronous firing between the AMG and AC. Third, when examining the distribution patterns in the synchrony matrix before noise trauma (seed Fig. 11A), the moderate level of synchrony existed between the rostral and caudal regions in the AMG and the entire AC indicates that there was no damage to any frequency regions in the AC. However, after noise exposure to induce tinnitus, the increased synchrony shifted to the high-frequency region in the AC and the increased synchrony occurred when the entire AMG was recorded (Fig. 11B–C). The shift towards the high-frequency region in the AC may be attributed to compensatory gain as a result of damage to the high-frequency region. However, it is not clear why the entire AMG was involved in the increased synchrony with the AC. Nevertheless, the result implies that tinnitus may involve auditory attention, especially sharp and annoying perceptions to high-frequency tones (Zwicker and Fastl, 1990). Taken together, these findings suggest that the AMG may actively interact with the AC in the etiology and

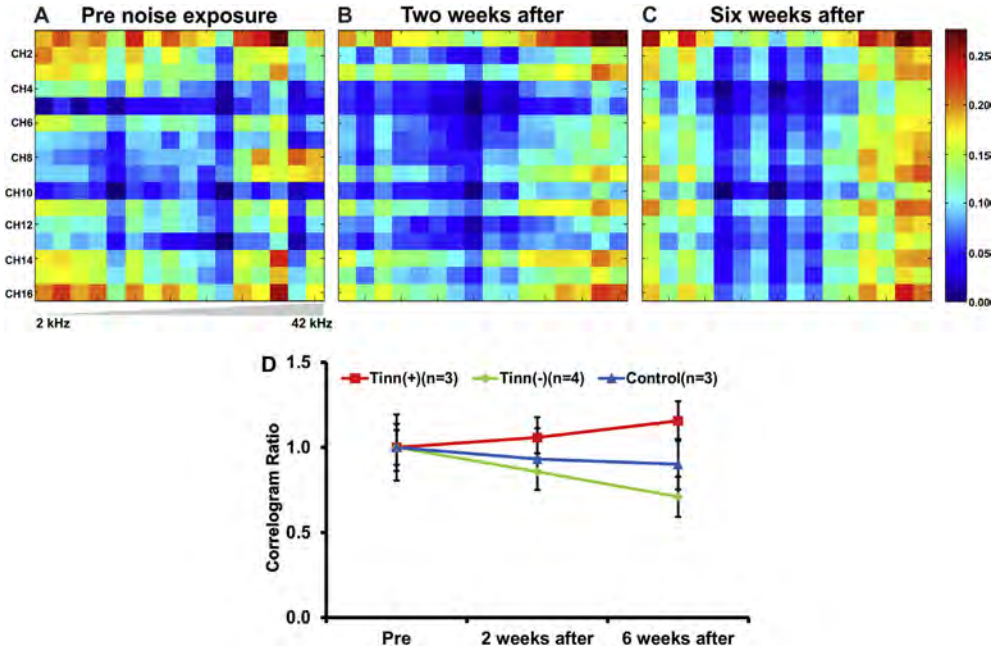


**Fig. 11.** A–C. Neurosynchrony as revealed by correlogram rate matrix between the AC and AMG of tinnitus$^{(+)}$ group. The matrix provides the visualization and evaluation of neurosynchrony of multi unit recording from different channels. The resultant grid displays the reference channel (y-axis) vs. target channel (x-axis), with the z-axis color proportional to the degree of correlation. The Y axis represents the data from the AMG and the X axis represents the data from the AC. The correlogram rate significantly increased after noise lesion. D. Changes in the normalized correlogram rates between the AC and the AMG of anesthetized rats. The correlogram ratio of the tinnitus positive group significantly increased after noise lesion compared to tinnitus negative and control groups.

perception of tinnitus.

## 6. Conclusions

Tinnitus is often accompanied by anxiety, increased irritability, sleep disturbance, and emotional distress, although their relationship with tinnitus may not be totally linear. This illustrates the active involvement of limbic-associated dysfunctions in the etiology and perception of tinnitus. This paper reviewed the psychophysical evidence and neural activity related to noise-induced tinnitus that we found in the projects funded by the Tinnitus Research Consortium.

Behaviorally, we have tested for tinnitus by using different paradigms such as a conditioned suppression/avoidance paradigm, gap detection acoustic reflex behavioral paradigm, and our newly developed conditioned licking suppression paradigm. Each of the above paradigms has strengths and weaknesses. The new tinnitus behavioral paradigm possesses several strengths, including relatively short baseline training requirements, frequency specification of tinnitus perception, and sensitive tinnitus testing at the individual level. To test for tinnitus-related limbic dysfunctions, we used elevated plus maze and Morris water maze to determine whether tinnitus positive rats displayed greater anxiety and cognitive impairment, respectively. We found that the majority of rats with highest anxiety levels had tinnitus. We did not find spatial cognitive deficits in tinnitus positive or negative rats, which reflect the clinical population where only certain tests have uncovered cognitive dysfunction in a portion of tinnitus subjects.

Immunocytochemically, we found that hamsters with evidence of tinnitus manifested increased FLI in the contralateral lateral lemniscus, and bilateral central nucleus of the inferior colliculus and AC. The fact that we did not find increased FLI in the lower brainstem structures suggests that they may be involved in acute tinnitus whereas the midbrain and cortex are involved in more chronic tinnitus. At the same time, we found that animals with tinnitus manifested increases in FLI in many autonomic brain structures, and structures involved in behavioral responses to stress, arousal and attention and fear-conditioning.

Electrophysiologically, we found that rats with tinnitus developed increased spontaneous firing and neurosynchrony in the AC. This emphasizes the notion that the tinnitus percept is of cortical origin and that hyperactivity and synchronous firing within the AC are important neural correlates of tinnitus. Such increased spontaneous firing and neurosynchrony were also found in the AMG of rats with tinnitus. Furthermore, inter-auditory (AC) and non-auditory (AMG) structural neurosynchrony were increased in rats with tinnitus. The increased synchrony predominantly occurred between the high-frequency regions of the AC and the entire AMG over time. These findings suggest that tinnitus may be actively produced and maintained by the interactions between the AC and AMG.

Taken together, our results suggest that the chronic tinnitus involves both auditory and non-auditory structures, and that the limbic system plays an important role in tinnitus perception. These findings further support treatment strategies that modulate neural activity in both auditory and non-auditory systems.

## Acknowledgments

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