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Tinnitus tends to occur in people who have a degree of hearing loss, which itself is associated with a wide range of changes in the structure, chemistry and function of many parts of the brain. Many studies on tinnitus to date have compared groups of patients or animals with tinnitus to controls unmatched for hearing levels. These have shown striking differences, but cannot demonstrate which of these simply relate to hearing loss and which, if any, are specific to tinnitus. Fortunately, this issue is now widely recognised, with positive steps being taken to separate correlates of tinnitus from those of hearing loss or other confounds.

This summary of new research findings in 2016 begins with those that seem to contradict the results of previous less carefully controlled studies. Next, it highlights key advances in our ability to study tinnitus, on account of greater understanding of its relationship with hearing loss and improved ways of determining whether animals are experiencing tinnitus. Finally, it discusses advances in understanding of how tinnitus relates to changes in the auditory (hearing) pathway and wider parts of the brain.

Two steps forward, one step back
A popular theory of tinnitus is that hearing loss leads to reduced input to parts of the brain’s hearing pathway, which causes the gain (or ‘volume dial’) to be turned up to compensate. The gain is also turned up on spontaneous firing of brain cells, leading to increased firing rates that result in the perception of sound. Previous work has shown that animals with tinnitus induced by hearing loss do indeed show such increases in nerve firing. However, hearing loss itself is associated with such changes. A new study by Longenecker and Galazyuk [1] addressed this issue by causing standardised noise damage in sixteen mice, and determining which ones did and did not show evidence of tinnitus. The researchers made the additional advancements of making recordings from the auditory midbrain (an early hearing centre) with the animals awake, and therefore presumably experiencing tinnitus, rather than anaesthetised. They found that all the animals showed increased nerve firing rates, irrespective of tinnitus, and also that another pattern of altered nerve firing previously attributed to tinnitus, called...
‘bursting’, occurred in some animals that did not show evidence of tinnitus, and failed to occur in some animals that did. While this was just one relatively small study, and requires further corroboration, it does suggest that these processes alone are unlikely to be the principal basis for tinnitus in the brain.

In humans, it is rarely possible to measure spontaneous electrical brain activity except at a high level in the brain – the cerebral cortex. Synchronised rhythmic firing of very large numbers of brain cells produces oscillations – or ‘brainwaves’ – that can be detected using electroencephalography (EEG). However, there are other strong sources of electrical activity on the scalp, including movements of the muscles and eyes. The last decade has seen many studies reporting abnormal oscillations at the scalp over the auditory (hearing) parts of the brain, and even most of the rest of the scalp, which in some studies have been very dramatic. These changes have appeared to be able to distinguish tinnitus patients from controls, and to correlate with tinnitus severity and other markers. This has led to high hopes for the use of EEG as both a diagnostic test for tinnitus, and as a biomarker of response to treatment. However, a recent study by Pierzycki and colleagues [2] has cast doubt over the usefulness of EEG in this regard. This study featured a larger sample of tinnitus patients than most previous similar studies, and tested each participant on two separate occasions. The results showed good correspondence between each participant’s recordings from the two sessions (suggesting that the results were reliable), but no significant relationship between any type of recorded activity and any aspect of the tinnitus experience. The major limitations of the study were that it did not feature a non-tinnitus control group, and that it only looked at average electrical activity over the whole scalp, rather than anything specific to a particular area or brain location. However, at present it seems doubtful that the very striking differences in electrical activity at the scalp previously attributed to tinnitus are actually meaningful. Future similar studies will need to use much more subtle, nuanced measures, as well as demonstrating reliability across multiple studies.

For over a decade there has been substantial interest in whether changes in the physical structure of the brain (e.g. specific areas of loss or gain of brain cells) might affect the risk of developing tinnitus, or occur as consequences of longstanding tinnitus. However, perhaps partly due to a varied range of research methods and tinnitus patient characteristics, the findings of different studies have been starkly contradictory of each other, without any consistent findings emerging. Sadly, this year has been no different, with one large study showing localised brain changes in association with duration of tinnitus [3] but another large study [4] showing striking widespread changes on account of age but no changes attributable to tinnitus once age had been accounted for.

Figure 1
Areas of altered thickness or the brain (red = increased, blue = decreased) reported to occur with increasing duration of tinnitus in the left hemisphere of the brain [3]

Figure 2
Areas of altered thickness of the brain occurring with age, with layout and colour scales as for previous figure. Once age was accounted for, no changes attributable to tinnitus duration were observed. [4]
Yet another large study, by Allan and colleagues [5], comparing tinnitus patients to controls carefully matched for age and hearing found only very small differences, most of which were contradictory to results of previous studies.

**Hearing loss**
Recent studies have shown that when two groups of age-matched volunteers have been compared – one with tinnitus and normal audiograms (standard hearing tests), and the other with no known tinnitus or hearing problem – the tinnitus group have shown evidence of ‘hidden’ hearing loss. This has been demonstrated in the form of reduced electrical responses to sound stimulation generated by the auditory nerve [6] [7]. This hidden hearing loss was thought to underlie tinnitus. New findings have revealed that the situation is more complicated than this. Two similar studies in the past year have focused on volunteers with tinnitus and normal audiograms, with one checking that even the very highest frequencies (normally omitted from testing) were matched between groups. One of these studies, by Konadath and colleagues [8], found that electrical responses from both the auditory nerve and midbrain were reduced in the tinnitus group, therefore showing hidden hearing loss but not the compensatory increases in central gain believed to underlie tinnitus generation. The other study, by Guest and colleagues [9], found no differences in auditory nerve or brain responses between groups, though it did find a greater history of previous noise exposure in the tinnitus volunteers. Rather than recruit groups with and without tinnitus, and search for differences between them, a new study by Gilles and colleagues [10] took the different approach of recruiting a group of young adults with symptoms of hearing loss due to recreational noise exposure, and then grouping the volunteers according to whether or not they experienced ongoing tinnitus. They tested various aspects of their hearing, and could detect no difference between the two groups in standard hearing tests, including the very high frequencies, nor other clinical measures including electrical auditory nerve responses. Therefore, the degree of hearing loss of any of these types did not seem to be the deciding factor in who developed tinnitus. What the study did find was that the tinnitus group were slightly, but significantly, worse at correctly hearing speech in the presence of background noise.

Another approach being taken is to consider two major types of nerve fibres connecting the cochlea to the brain. The first type are the low-threshold fibres, which are activated by even quiet sounds and form the basis of standard audiogram results. The second type are high threshold fibres, which are activated only by louder sounds. Because loud sounds are infrequent and short-lived in nature, these fibres are not adapted for long periods of activation and are therefore vulnerable to damage or death if activated for too long. A study by Paul and colleagues [11] has measured responses in tinnitus patients and controls with matched audiograms, and used computer modelling of the results to show that tinnitus patients tend to have relatively greater damage to these high threshold auditory nerve fibres. In summary, there have been significant advances in our understanding of the relationship between hearing loss and tinnitus, but a consistent pattern has yet to emerge.

**Animal models**
Animal tinnitus studies allow very detailed assessments of structure or function in any part of the brain. However, to date they have been hampered by two main limitations in actually being able to attribute any observed changes to tinnitus itself: the difficulty in assessing whether an animal is experiencing tinnitus, and the tendency to compare groups of animals with tinnitus plus hearing damage to control groups with undamaged hearing. However, recent improvements in experimental techniques have made major progress towards addressing these issues. Some studies have focused on improving conditioned behaviour methods, where animals are taught to perform certain tasks either in the presence of sound or quiet [12] [13]. Others have used the automatic startle response elicited by unexpected sounds, which does not require lengthy prior training of the animals. Previous versions of this method had been
confounded by changes in this response on account of hearing loss itself and its other consequences such as hyperacusis, and deficits in processing the precise timing of sounds. Now, a group of researchers has carefully disentangled these separate effects, and shown that there are aspects of the startle response changes that appear to be uniquely associated with tinnitus as opposed to confounding factors [14]. Separately, the research group of Jeremy Turner, who originally developed the startle response method, has also used a refined form, examining animals shortly before tinnitus onset, soon after, and 12 months later [15]. They found that long or very intense periods of noise damage were more likely to cause hyperacusis, and longer or milder periods of noise overexposure were more likely to cause tinnitus. While these findings are in themselves interesting and useful for understanding tinnitus, the main gains should accumulate over time as these refined methods are adopted in other studies of brain changes in tinnitus.

One new approach being facilitated by refined animal models is to focus on genetics rather than brain structure or activity. Yu and colleagues [16] studied mice with and without a mutation in a gene called GLAST, which regulates the balance of excitation and inhibition. They then applied salicylate, a drug known to cause tinnitus in overdose, and found greater behavioural evidence of tinnitus in mice with the mutation. It remains to be seen how applicable these findings are to noise-induced tinnitus, and to humans, but this potentially opens a new avenue to investigate mechanisms and treatments for tinnitus.

Auditory (hearing) pathway and beyond

A good example of a recent animal study to carefully distinguish between equivalently hearing damaged animals with and without evidence of tinnitus was one by Wu and colleagues [17]. In a study of guinea pigs with induced hearing loss, they found increased rates of nerve firing and synchrony in the first auditory processing centre in the brain – the dorsal cochlear nucleus – in the tinnitus animals over and above controls. While such changes have also been observed with hearing loss irrespective of the presence of tinnitus, this evidence strengthens the case for them forming at least part of the basis of tinnitus. Further up the auditory pathway in the auditory midbrain, rather than trying to correlate spontaneous brain activity with the presence of tinnitus, Smit and colleagues applied rhythmic electrical stimulation to animals that had shown behavioural evidence of tinnitus [18].

They found that this treatment – called deep brain stimulation (DBS), which applied elsewhere in the brain already has a role in treating disorders such as certain cases of Parkinson’s disease – eliminated evidence of tinnitus. Interestingly, the same group of researchers [19] looked at patients with tinnitus undergoing DBS for coexisting Parkinson’s disease.

Although the areas targeted were all outside of the auditory system, they found that DBS treatment to a particular area called the subthalamic nucleus (STN) significantly reduced tinnitus loudness in certain individuals.
This highlights the importance of additional brain circuitry in tinnitus, beyond the auditory pathway or areas interacting with it. Another study to examine the influence of auditory and wider brain networks on tinnitus was performed by Vanneste and colleagues [20]. In this, they studied EEG ‘brainwave’ signals recorded from a large group of tinnitus patients while they rested. They categorised patients depending on their level of hearing loss, and found two key differences in brain activity: patients with less hearing loss showed more on-going activity in part of the auditory cortex, while patients with more hearing loss had more on-going activity in a memory centre called the parahippocampal cortex.

The researchers interpreted this as evidence of the tinnitus signal being generated differently - in the hearing system, or retrieved from memory – depending on the degree of hearing loss. However, other interpretations are possible. Although a control group was included, these non-tinnitus volunteers had no known hearing loss, so it remains to be seen whether similar activity patterns are seen in association with different levels of hearing impairment in patients without tinnitus. Perhaps in keeping with this result, the results of another study by Hong and colleagues [21], has suggested that abnormal generation of internal predictions, which are fundamental to normal perception, may be involved in tinnitus. This focused on the brain’s ‘P300’ response, which occurs following unexpected events such as sounds, and found it to be smaller in patients with tinnitus, and to show an altered pattern of communication between the brain centres that generate this response. Collectively, these findings suggest that the brain mechanisms responsible for tinnitus may include both generators in the auditory pathway, and wider networks that modulate this activity and may even make the difference between whether it gets perceived as sound or not. Further research should aim to build upon these findings by generating more specific hypotheses, and running studies that support, refute or refine these.

Figure 4
Changes in resting-state ‘brainwaves’, compared to normal hearing non-tinnitus controls, in tinnitus with relatively little hearing loss (top row) and tinnitus with severe hearing loss (bottom row). Coloured areas indicate increased strength of brainwaves in the tinnitus group.[20]
References


