Abnormal Brain Activity in an Animal Model: Closing the Loop on Tinnitus

BY MICHAEL B. CALFORD, PH.D., UNIVERSITY OF NEWCASTLE, AUSTRALIA
AND CARL H. PARSONS, PH.D., UNIVERSITY OF WESTERN SYDNEY, AUSTRALIA

The cochlea, a spiral-shaped part of the inner ear, processes sound by transforming it from physical vibrations (like the bass rhythm one might feel at a concert) into "electrochemical" signals that the brain interprets as sound. These vibrations activate different neurons (cells) in the ear depending on the frequency of the incoming sound. High frequency sounds vibrate the outside of the cochlea's spiral; low frequencies vibrate the inside. This pattern of neural stimulation repeats throughout the hearing pathways of the brain. This means that different cells in the brain respond to different frequencies, just like ear cells do.

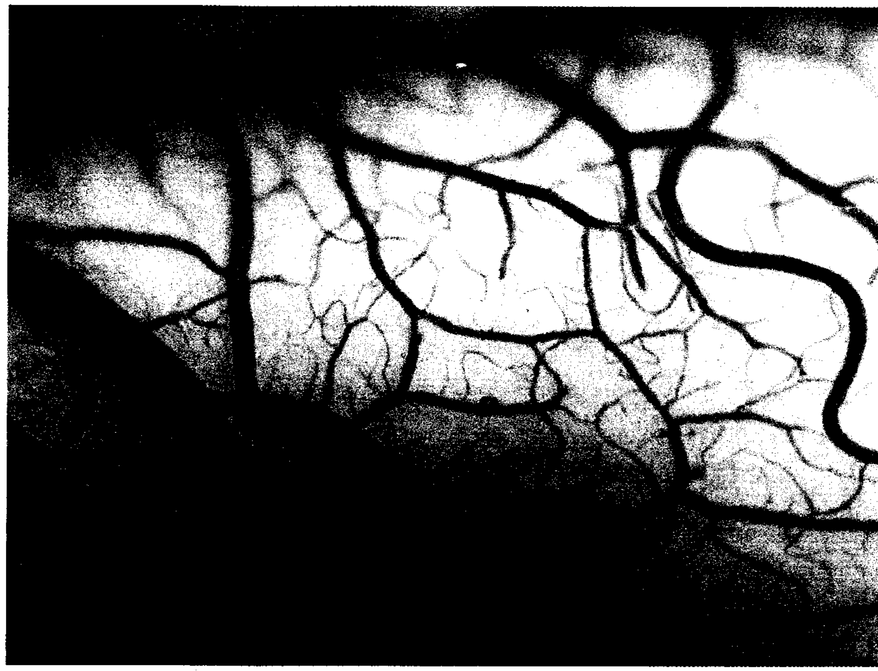

Figure 1. A close-up view of the auditory cortex, a part of the brain that processes sound.

Mapping sound frequencies in the brain

The processing of sound by the brain takes place at multiple sites - from the brainstem through to the cerebral cortex. The connections between these sites form a distinct pathway along which sound is processed. Each site along the pathway has its own "maps" for registering frequencies. It is a common misunderstanding that parts of the auditory pathway that respond to low, medium or high frequency sounds connect exclusively with other parts of the brain that respond to low, medium or high frequency sounds, respectively. In fact, the connections between the various auditory processing sites of the auditory pathway give only a rough template for these frequency maps. Nevertheless, in the working brain, the maps for registering sound frequency are very precise. This transformation from a rough template in connection to a precise frequency processing map is possible because the activity of neurons can be reinforced or suppressed by complex brain circuits at each level. Nearby neurons responding to the same frequencies are reinforced, whereas nearby neurons responding to different frequencies are suppressed. Repetition of these simple rules thousands of times at millions of neurons produces the precise maps of frequency processing. Disruption of the normal operation of these circuits, particularly at higher levels of the brain, provides a plausible basis for many cases of tinnitus.

An analogy for these frequency maps is the way that the body also connects to multiple levels of the brain. In other words, our brain has "body-surface maps" that register different parts of the body. When a limb, such as an arm, is lost or amputated, amputees often report the sensation of a "phantom limb." This is because parts of the brain that previously registered perceptions of the arm are still intact but the loss of the nerve inputs from the arm disrupt and distort neural-circuits responsible for the body-surface map. This produces abnormal activity in the body surface

continued on page 22

Abnormal Brain Activity in an Animal Model: Closing the Loop on Tinnitus

continued from page 13

map, which the brain interprets as coming from the missing arm. In many cases, stimulating other parts of the body – such as the shoulder, or even the face – produces dual perceptions: the real stimulation of the shoulder/face and the phantom stimulation of the missing arm. Our model is that, after mild damage to the cochlea, tinnitus results from similar events in the auditory processing area of the cerebral cortex (termed the auditory cortex)(Fig.1). In other words, parts of the brain are responding to the "missing ear nerves."

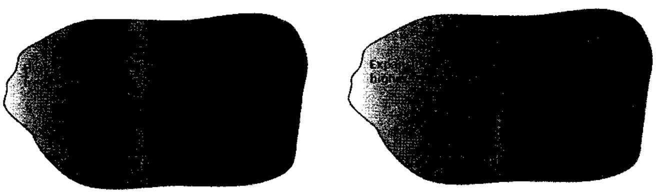

Figure 2: This diagram illustrates the brain's response to sound following hearing damage. The wrong parts of the brain begin responding to certain frequencies, likely resulting in tinnitus.

Tinnitus and the phantom limb phenomenon

In previous animal experiments, our team damaged a limited area of the subject's cochlea, thereby preventing the ear from transmitting a certain range of sound frequencies to the brain. This is akin to an arm amputation. And similar to stimulating the shoulder or face, and feeling the phantom arm, we found that sound frequencies close to the damaged area will activate areas of the auditory cortex that, because of the cochlear damage, shouldn't be responding. To return to the map analogy, prior to cochlear damage, each part of the auditory cortex responded only to sounds that matched its place on the frequency map. Following cochlear damage, these areas responded to signals that were off their place in the frequency map (Fig. 2).

Our experimental program is not yet complete. However, we have "closed the loop" by demonstrating that rats with noise-induced tinnitus have an over-representation of sound frequencies adjacent to those directly affected by the noise damage. The disruption of these brain circuits, which normally act to preserve a precise frequency map, leads to this unusual brain activation. Behavioral testing shows that the rats perceive this unusual activation as tinnitus.

Reducing the effects of tinnitus

The next stage is to use this animal model and our recoding of abnormal brain activity to examine if some interventions or potential treatments can reduce the tinnitus. We can test the same sort of strategies, based upon patterned sound stimulation, that other investigators are now proposing as experimental treatments for human tinnitus. A positive outcome would be to show that the auditory cortex can be retrained to generate a frequency map appropriate to its altered input. This is to say, we hope to retrain the brain so that, although it is not receiving a full range of sound frequencies from the ear, it is only responding where it should and not in adjacent areas.

However, we know that these maps in adult brains are very stable and it is difficult to induce changes from sound stimulation. In contrast, the frequency maps of young animals are easily altered by experience. Hence, retraining in the adult brain attempts to recreate events that are normally limited to the very young brain.

To make the adult auditory cortex act like that of a young animal, we are experimenting with stimulating known "modulation pathways" of the brain, which, in normal development, release chemicals that enable experience-mediated changes. At a later stage, we will couple drugs that may help enhance modulation with sound stimulation. We hope that, together, drugs and sound stimulation will retrain the auditory cortex, decrease the abnormal stimulation and, hence, reduce the tinnitus. (((

Professor Michael Calford is Pro Vice-Chancellor and Head of The Faculty of Health at the University of Newcastle, Australia.

Dr. Carl Parsons is a Lecturer in Anatomy and Cell Biology in the School of Medicine at the University of Western Sydney, Australia.