No auditory experience, no tinnitus: Lessons from subjects with congenital- and acquired single-sided deafness

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ABSTRACT

Recent studies have adopted the Bayesian brain model to explain the generation of tinnitus in subjects with auditory deafferentation. That is, as the human brain works in a Bayesian manner to reduce environmental uncertainty, missing auditory information due to hearing loss may cause auditory phantom percepts, i.e., tinnitus. This type of deafferentation-induced auditory phantom percept should be preceded by auditory experience because the fill-in phenomenon, namely tinnitus, is based upon auditory prediction and the resultant prediction error. For example, a recent animal study observed the absence of tinnitus in cats with congenital single-sided deafness (SSD; Eggermont and Kral, Hear Res 2016). However, no human studies have investigated the presence and characteristics of tinnitus in subjects with congenital SSD. Thus, the present study sought to reveal differences in the generation of tinnitus between subjects with congenital SSD and those with acquired SSD to evaluate the replicability of previous animal studies. This study enrolled 20 subjects with congenital SSD and 44 subjects with acquired SSD and examined the presence and characteristics of tinnitus in the groups. None of the 20 subjects with congenital SSD perceived tinnitus on the affected side, whereas 30 of 44 subjects with acquired SSD experienced tinnitus on the affected side. Additionally, there were significant positive correlations between tinnitus characteristics and the audiometric characteristics of the SSD. In accordance with the findings of the recent animal study, tinnitus was absent in subjects with congenital SSD, but relatively frequent in subjects with acquired SSD, which suggests that the development of tinnitus should be preceded by auditory experience. In other words, subjects with profound congenital peripheral deafferentation do not develop auditory phantom percepts because no auditory predictions are available from the Bayesian brain.

1. Introduction

Non-pulsatile tinnitus is a common otological symptom, characterized by a conscious auditory perception in the absence of an external stimulus; this is often called a ‘phantom sound’ because there is no corresponding genuine physical source of the sound (Jastreboff, 1990). Although previous researchers have suggested possible mechanisms of the development of tinnitus that can be summarized into 3 broad categories: 1) peripheral auditory deafferentation and central maladaptive plastic changes, 2) spontaneous neuronal hyperactivity, and 3) increased cross-fiber synchrony (Preece et al., 2003; Eggermont and Roberts, 2012; Tyler, 2006), the exact pathophysiology of tinnitus has yet to be clearly elucidated. A recent study suggested that an established tonotopic map that leads to a corresponding auditory memory is necessary to generate tinnitus (Eggermont and Kral, 2016). According to a similar concept, the Bayesian brain model, the brains of subjects with peripheral hearing loss-induced auditory deafferentation constantly generate predictions about the environment to minimize sensory uncertainty that results from a limited amount of auditory information (De Ridder et al., 2014a). Thus, phantom auditory perceptions following auditory deafferentation are the
consequence of an active process during which the brain updates predictions. From this perspective, sensations due to both external stimuli and prediction-driven interpretation and organization are required for the perception of tinnitus (Joos et al., 2014). Previous human studies have reported a relationship between tinnitus pitch and maximum hearing loss frequency, which suggests that tinnitus is a fill-in phenomenon for homeostasis (Norena et al., 2000; Schaette et al., 2012; Schecklmann et al., 2012). In other words, missing auditory information due to hearing loss can induce auditory phantom percepts that correspond to the missing auditory information (De Ridder et al., 2014a; McMillan et al., 2014). Thus, tinnitus can be explained as an intentional compensatory auditory perception. In a recent study, subjects with tinnitus and severe acquired hearing loss exhibited increased cortical activity in the parahippocampal gyrus relative to non-tinnitus controls, and it was suggested that this increase may be associated with abnormal activity aimed at reducing environmental uncertainty (Vanneste and De Ridder, 2016).

Because environmental uncertainty is based on auditory experience, tinnitus may not be generated without prior auditory experiences. Using an animal model of congenital single-sided deafness (SSD), a recent investigation failed to find evidence of auditory phantom percepts in the deaf ear (Eggermont and Kral, 2016). This result suggests that auditory deafferentation that induces phantom percepts should be preceded by auditory experience because the fill-in phenomenon is based upon an auditory prediction and the resultant prediction error (Eggermont and Kral, 2016). To the best of our knowledge, no human studies have investigated the presence and characteristics of tinnitus in subjects with congenital SSD. Thus, the present observational study aimed to determine the presence and characteristics of tinnitus in human SSD subjects to evaluate the replicability of the abovementioned animal study. The present study sought to determine the role that auditory experience plays in the development of tinnitus by analyzing and comparing the presence and characteristics of tinnitus in patients with congenital with those in patients with acquired SSD.

2. Materials and methods

2.1. Participants

This study retrospectively reviewed the records of patients with congenital or acquired SSD who visited the outpatient clinic at Seoul National University Bundang Hospital between January 2016 and December 2016. SSD was defined as follows: (1) pure-tone average of 500, 1000, 2000, and 4000 Hz greater than 90 dB hearing level (dB HL) in the affected ear in conjunction with (2) pure-tone average at the same frequencies lower than 20 dB HL in the non-affected ear. Patients with the uncertain subjective onset of hearing loss, radiological abnormalities (such as a unilateral enlarged vestibular aqueduct) that may have resulted in progressive SSD, or a history of operations or auditory interventions for the treatment of hearing loss were excluded from the study; ultimately, 20 subjects with congenital SSD were enrolled.

After meticulous reviews of subject history, laboratory tests, radiological evaluations, and medical records, seven subjects who had definite clinical or radiological evidence of congenital SSD were classified as “definitely congenital” SSD; this group included a documented congenital infection with the mumps virus (one subject) and several cases of unilateral cochlear nerve deficiency (six subjects). The remaining 13 subjects who did not have definite evidence of a congenital onset but exhibited the subjective onset of hearing loss as “under school age” or “childhood” were classified as “probably congenital” SSD. Subjects with no definite evidence of congenital onset or the ambiguous subjective onset of hearing loss (e.g., “more than 20 years ago”) were excluded from the analysis. The acquired SSD group included 60 patients with no history of tinnitus prior to the onset of idiopathic sudden sensorineural hearing loss (ISSNHL), who were recruited during a retrospective random screening of recently visited patients. None of the subjects in the acquired SSD group had a history of objective tinnitus or etiologies such as Meniere’s disease, head injury, brain surgery, or neurological disorders. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board and was conducted in accordance with the Declaration of Helsinki (IRB-B-1703-385-105).

2.2. Audiological and psychoacoustic evaluations

At the initial visit, a structured history of the characteristics of tinnitus on the affected side and the psychoacoustic nature (pure-tone or narrow-band noise) of the tinnitus were obtained. All subjects underwent pure-tone audiometry (PTA) testing that included psychoacoustic tests of tinnitus such as tinnitus pitch matching, tinnitus loudness matching, and the minimum masking level test. The hearing thresholds for seven different octave frequencies (0.25, 0.5, 1, 2, 3, 4, and 8 kHz) were evaluated using PTA in a soundproof booth, and each subject’s audiometric configurations were classified into the following three categories based on the PTA results: flat, i.e., thresholds across frequencies did not vary more than 20 dB from each other; high tone, i.e., thresholds showed levels equal to or lower than 250–8000 Hz, and differences between the thresholds at 250 and at 8000 Hz were more than 20 dB; and low tone, i.e., thresholds showed at equal or higher levels from 250 to 8000 Hz and the differences between the thresholds at 250 and 8000 Hz were more than 20 dB (Liu et al., 2011). The mean hearing threshold was calculated using the average of the hearing thresholds at 0.5, 1, 2, and 4 kHz, and the frequency of each subject’s maximum hearing loss was determined based on the results of the PTA. In cases where maximum hearing loss was evident at multiple frequencies, the lowest such frequency was recorded. The range of SSD was determined by summing up the audiometric frequencies with a threshold >70 dB (Vanneste and De Ridder, 2016). Due to poor compliance, 16 subjects in the acquired SSD control group were not screened using the tinnitusgram, and as a result, the analysis of tinnitus characteristics included 44 subjects from the acquired SSD group.

2.3. Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences software (SPSS 22.0 K, IBM; Seoul, Korea). To determine significant differences between the two groups in the screened continuous and categorical variables, independent t-tests, Chi-square tests, and linear-by-linear association analyses were performed, as appropriate. To analyze the relationships between the audiometric variables and the tinnitus characteristics, Spearman’s correlation analysis were performed. P-values <0.05 were considered to indicate statistical significance.

3. Results

3.1. Demographic characteristics

Subjects’ demographic and clinical characteristics are summarized in Table 1. There were no significant differences between the two groups, except in terms of the SSD etiology: subjects in the acquired SSD control group had idiopathic SSD, whereas those in the congenital SSD group included cases of congenital SSD.
congenital SSD group experienced tinnitus in the SSD ear (Fig. 1(a)),
and those in the normal ears were 15.3 \pm 7.8 dB (Fig. 3(d) and (e), respectively), but there was no significant correlation between tinnitus pitch and the frequency of maximum hearing loss (Fig. 3(f)).

### 3.2. Presence of tinnitus

The presence and characteristics of tinnitus for the two groups are presented in Table 2. Remarkably, none of the 20 subjects in the congenital SSD group experienced tinnitus in the SSD ear (Fig. 1(a)), whereas 30 of 44 subjects (68.2%) with acquired SSD did. Additionally, there were positive correlations between the audiometric characteristics and psychoacoustic characteristics in the acquired SSD subjects with tinnitus. These results replicate those of a previous animal study, which reported that the establishment of a tonotopic map is a prerequisite for tinnitus generation (Eggermont and Kral, 2016). Also, these results may be not be perfectly explainable by previous theories of tinnitus generation such as peripheral auditory deafferentation and central maladaptive plastic changes, spontaneous neuronal hyperactivity, or increased cross-fiber synchrony.

### 4. Discussion

To the best of our knowledge, the present study is the first to explore the role of auditory experience in the development of tinnitus in humans. The present findings showed that none of the subjects with congenital SSD perceived tinnitus on the SSD side, whereas 30 of 44 subjects (68.2%) with acquired SSD did. Additionally, there were positive correlations between the audiometric characteristics and psychoacoustic characteristics in the acquired SSD subjects with tinnitus. These results replicate those of a previous animal study, which reported that the establishment of a tonotopic map is a prerequisite for tinnitus generation (Eggermont and Kral, 2016). Also, these results may be not be perfectly explainable by previous theories of tinnitus generation such as peripheral auditory deafferentation and central maladaptive plastic changes, spontaneous neuronal hyperactivity, or increased cross-fiber synchrony.

### 4.1. Absence of tinnitus in the congenital SSD ear

Recent studies have proposed that the generation of a phantom auditory percept results from active feedback looping in the brain during compensatory efforts while dealing with hearing loss. That is, the brain constantly makes predictions about the environment to minimize uncertainty, which can be thought of as a comparison of actual input into the sensory system (signal) versus internal representations of previous input (memories) (De Ridder et al., 2014a; De Ridder et al., 2011). From this perspective, in most patients with auditory deafferentation that results in tinnitus, the brain attempts to overcome deprivation in auditory input by generating auditory predictions via increases in topographically restricted tones, widening receptive fields, and rewiring dendrites and axons (De Ridder et al., 2014a). Furthermore, in the case of acquired profound hearing loss in which uncertainty cannot be compensated for by neural plasticity or tonotopic reorganization, uncertainty can be minimized by the retrieval of existing auditory memories stored in the parahippocampal gyrus (De Ridder et al., 2014a; Vanneste and De Ridder, 2016). However, few studies have investigated the absence of tinnitus in subjects with congenital auditory deafferentation. Understanding the impact of the total absence of auditory experience, such as congenital deafness, is of the utmost importance because even a brief period of hearing...
Fig. 1. Representative audiograms illustrating the absence of tinnitus in subjects with congenital single-sided deafness (SSD). (a) Pure-tone audiometry (PTA) results of a 43-year-old male subject with left “probably congenital” SSD. The subject denied the presence of tinnitus on both sides. (b) PTA results of a 55-year-old male subject with right “probably congenital” SSD. The subject complained of tinnitus on the left side (8 kHz, loudness = 4 dB hearing level [dB HL]).

Fig. 2. Representative audiograms showing the presence of tinnitus in subjects with acquired single-sided deafness (SSD). A 30-year-old male subject with left acquired SSD due to idiopathic sudden sensorineural hearing loss (ISSNHL) and (a) a 45-year-old male subject with left acquired SSD due to ISSNHL with complaints of ipsilesional tinnitus.

Fig. 3. Spearman’s rank-order correlation analyses between tinnitus characteristics and audiometric variables in subjects with acquired single-sided deafness (SSD). Significant positive correlations were revealed between mean hearing threshold and the range of SSD ($p = 0.52$, $p = 0.03$) (a), between hearing loss at the tinnitus pitch and the range of SSD ($p = 0.41$, $p = 0.027$) (b), between hearing loss at the tinnitus pitch and the mean hearing loss ($p = 0.52$, $p = 0.003$) (c). The mean and maximum hearing loss were positively correlated with tinnitus loudness ($p = 0.44$, $p = 0.015$ and $p = 0.76$, $p < 0.001$, respectively) ((d) and (e), respectively). However, there was no significant correlation between tinnitus pitch and the frequency of maximum hearing loss (f).
experience may affect the maturation of auditory pathways (Schramm et al., 2002).

A recent study employing a cat model of unilateral congenital deafness in which hair cells are lacking due to dysplasia in the organ of Corti reported that spontaneous firing rates in the auditory cortex were significantly reduced relative to normal hearing controls, which suggests the absence of tinnitus in congenitally deaf ears (Eggermont and Kral, 2016). Thus, auditory perception requires previous auditory experience. In line with the findings of that animal study, the present study found that none of human subjects with congenital SSD who had never had any auditory experiences in the affected ear perceived tinnitus on the SSD side, whereas 30 of 44 subjects with acquired SSD experienced tinnitus on the affected side. The present study was the first to demonstrate that, in human subjects with SSD, auditory experience is a prerequisite for tinnitus by comparing tinnitus perception between patients with congenital and acquired SSD. Additionally, the absence of tinnitus in the congenital SSD ear can be explained by the Bayesian brain model. Due to the absence of auditory input through the congenital SSD ear, a tonotopic map cannot be formulated in the affected side due to the lack of cortical activities in brain regions corresponding to the deaf ear (Eggermont and Roberts, 2012). In other words, somatic memories would not be established due to the absence of the active use of cortical areas (Eggermont, 2007; Eggermont and Roberts, 2004).

In Fig. 4(a) and (b), the differences of tinnitus development between congenital SSD and acquired SSD are schematically illustrated. Auditory predictions that minimize uncertainty in the brain can be updated by active sampling from the environment during previous auditory experiences (De Ridder et al., 2014a; Knill and Pouget, 2004) (Fig. 4(a)). However, in the absence of auditory experiences, auditory prediction cannot develop because the lack of actual input leads to an inability to compensate for uncertainty using the fill-in phenomenon (Fig. 4(b)). Prediction error that results from comparisons of expectations and actual external stimuli within mature neural circuitry acts as a driving signal for auditory perception. Because the maturation of neural circuitry underlying auditory perception is mainly determined by the statistics of sensory input (Kral, 2013), the neural circuitry supporting the interaction between lower-order (peripheral auditory input) and higher-order (prediction-driving process for auditory perception) auditory systems cannot develop (Kral et al., 2017). That is, deficits in this circuitry contribute to deficits in auditory perception, which in turn result in the absence of tinnitus in the congenital SSD ear. The absence of auditory experiences can also affect hippocampal plasticity both structurally and functionally. Considering that the hippocampal–auditory system is centrally involved in the formation of auditory memories, missing auditory input cannot be compensated for or retrieved from auditory memories stored in the hippocampus or parahippocampal gyrus in cases where auditory experience is lacking, resulting in the absence of tinnitus (Kraus and Canlon, 2012).

4.2. Development of tinnitus in acquired SSD ears

Of the 44 subjects in the present study with acquired SSD, 30 (68.2%) experienced tinnitus. The rate of tinnitus was similar to that observed in a previous study investigating the prevalence of tinnitus in ISSNHL patients (Muhlmeier et al., 2016). Thus, the present findings support the idea that auditory experience is an important prerequisite for the development of tinnitus. Meanwhile, cochlear implantation (CI) attenuates tinnitus in subjects with acquired SSD, but initiates tinnitus in subjects with congenital SSD (Cabral Junior et al., 2016; Kim et al., 2015; Song et al., 2013a, 2017; van Zon et al., 2015). The restoration of missing peripheral auditory input by CI in subjects with acquired SSD may reduce the necessity to compensate for prediction errors, whereas CI may introduce a novel tonotopic map in subjects with congenital SSD and result in tinnitus in some individuals due to the development of prediction error when the implanted device is turned off.

The present study also demonstrated that the psychoacoustic characteristics of tinnitus, such as loudness and pitch, were correlated with audiological characteristics in subjects with acquired SSD. The frequency range that covers hearing loss is associated with the characteristics of tinnitus, which suggests that tinnitus reflects a tonotopic representation within the auditory cortex (Sekiya et al., 2017; Vanneste and De Ridder, 2016). According to the Bayesian brain model, the brain generates predictions (neural firing in specific tonotopic regions) to reduce uncertainty (deprived auditory input to tonotopic regions in the auditory cortex), particularly in cases of mild hearing loss (Vanneste and De Ridder, 2016). However, in cases of profound hearing loss, where uncertainty cannot be overcome by neural plasticity or tonotopic reorganization in the auditory cortex, it can be minimized by the retrieval of existing memories (De Ridder et al., 2014a; Vanneste and De Ridder, 2016). This may be mediated by the parahippocampal gyrus, which is reciprocally connected with the auditory cortices (Munoz-Lopez et al., 2010) and is thought to be the sensory gate to hippocampal memories (Engelien et al., 2000). However, because the auditory cortex is tonotopically organized and the parahippocampal gyrus is

![Fig. 4.](image)
not, information transmitted from the hippocampal area to the auditory cortices may not be frequency specific, even though information in the range covering the hearing loss may be transmitted. This may explain the significant correlations between mean hearing loss and tinnitus loudness and between mean hearing loss and hearing loss at the tinnitus pitch, which were observed in the present study as well as previous studies (Vanneste and De Ridder, 2016). In contrast, the present study did not observe a significant correlation between perceived tinnitus pitch and maximum hearing loss frequency, in accordance with another previous study that also failed to reveal a relationship between the tinnitus pitch and the edge of high frequency hearing loss (Pan et al., 2009), which may have been due to the inability of the parahippocampal gyrus to transmit tonotopic auditory information. In that respect, the present study failed to replicate the findings of a previous study that reported a significant correlation between tinnitus pitch and frequency at maximal hearing loss (Schecklmann et al., 2012). This discrepancy may have been due to the different audiometric characteristics of the included subjects; the present subjects had profound hearing loss in the tinnitus ear, whereas most of the subjects assessed in the previous study showed mild high-frequency hearing loss.

4.3. Analogy to the somatosensory system

There are several analogies between tinnitus and pain in terms of pathophysiology, phenomenology, and clinical and treatment issues (De Ridder et al., 2011). The Bayesian brain model has also been used to explain the absence of phantom limb perceptions and the lack of phantom pain during the dream state (De Ridder et al., 2014b). Because this model predicts that a phantom percept is based on an internal model of the world and one’s own body, it can be acquired during ontogenetic development, or it can be genetically coded. In a large sample of 125 people with missing limbs, phantom experiences were present in 41 individuals who were either born limb deficient (n = 15; 12%) or who underwent amputation before the age of 6 years (n = 26) (Melzack et al., 1997). In contrast, none of the subjects in the present auditory study experienced phantom symptoms. In terms of the somatosensory system, it has been argued that phantom experiences provide evidence of a distributed neural representation of the body that is in part genetically determined. This might be in contrast to cochlear tonotopy, which is genetically coded, but not cortical tonotopy, which is formed through auditory exposure. Thus, there might be a fundamental difference between the somatosensory system, which encodes the bodily self and permits interactions with the environment to be embodied (Merleau-Ponty, 1945), and the auditory system, which does not directly encode an auditory self and therefore does not require a genetically determined representation in the brain.

4.4. Limitations and future perspectives

To the best of our knowledge, this is the first human study to demonstrate the causal role of auditory experience in the generation of tinnitus by comparing the presence and characteristics of tinnitus between patients with congenital SSD and those with acquired SSD. Although the present study provided an explanation for the generation of tinnitus, there are crucial limitations that should be addressed in future studies. First, the present study demonstrated the absence of tinnitus in congenital SSD ears and its presence in most acquired SSD ears, but found that some acquired SSD ears did not show tinnitus; this could not be explained by the Bayesian brain model. Although it is possible that there might be differences between acquired SSD ears with and without tinnitus in terms of activity in the auditory and non-auditory brain areas responsible for tinnitus generation and tinnitus-related distress (Kim et al., 2016; Song et al., 2013b, 2014, 2015a, 2015b), future studies should aim to reveal the cause of the absence of tinnitus in some acquired SSD ears. Second, the hearing level in subjects with tinnitus was evaluated using PTA at 250–8000 Hz. However, recent studies have shown that tinnitus can occur outside these clinical frequencies (Melcher et al., 2013); thus, future studies employing PTA at higher frequencies will be necessary. Third, although the present study discussed the role of auditory experience in tinnitus generation in subjects with profound auditory deafferentation in terms of reducing uncertainty, neuroscientific evidence from electrophysiological or functional neuroimaging studies are warranted to further support the present interpretations.

5. Conclusions

The present findings showed that tinnitus did not develop in congenital SSD ears, whereas most acquired SSD ears experienced tinnitus, indicating that the presence of tinnitus was determined by auditory experiences. Additionally, these observations replicated previous animal study suggesting that an established tonotopic map that leads to a corresponding auditory memory is necessary to generate tinnitus and also partially proved the Bayesian brain perspective with regard to the generation of tinnitus. In other words, auditory phantom perceptions cannot develop following congenital peripheral deafferentation, even if the damage is profound, because no auditory prediction can exist in the brain.

References