Current Trend of Treatment of Tinnitus and Hyperacusis

IFOS World Course, 2019

Dept. of Otolaryngology
Keio University
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1. Auditory abnormal sensation

2. Evaluation

3. Central management
Abnormal sensations

**Audition**
- tinnitus
- hyperacusis
  - autophony
  - phonophobia
- ear fullness
- paracusis
- diplacusis
- diplacusis loci
- auditory illusion

**Vison**
- floaters
- photopsia
  - photophobia
- blurred vision
- metamorphopsia
- visual illusion
Tinnitus

Definition

Perception of sound in the absence of environmental acoustic stimuli.

Prevalence

15% of the total population (36 million) experienced tinnitus. 20% out of them (7.2 million) have disabled tinnitus. 

The National Health Survey by Public Health Agency (1988)

25% of the total population (19 million) experienced tinnitus. 8% out of them (1.5 million) have tinnitus with severe annoyance.

The German Tinnitus League (1999)

1/4 of the total population (30 million) experienced tinnitus. 


= 20% (24 million)

= 3% (3~4 million)
Hyperacussis

Definition

Heightened sensitivity to sound, with aversive or pained reactions to normal environmental sounds.

(Steadman’s Medical Dictionary)

- sensitive hearing
- decreased sound tolerance
- phonophobia
- misophonia

• Hyperacussu: 20〜45% of Tinnitus
• Tinnitus: 80〜90% of Hyperacussis

Hyperacussis score

Annoyance of tinnitus

$r=0.575$
Difficulty in tinnitus management

1. subjective symptom
2. heterogeneity between tinnitus and hearing loss
3. peripheral vs central
4. annoyance
5. depression
6. no objective exam.
7. no basic treatment

- HL in tinnitus: 90%
- Tinnitus in HL: 50%

SNHL: 60〜80%
CHL: 20〜40%
Tinnitus: Case 1

- Bil. tinnitus with idiopathic progressive sensorineural hearing loss
- 32 y/o male
- Top researcher in the department of electric engineering of Tokyo Univ.
- Committed suicide 3 times
- Masker and psychotherapy
Tinnitus: Case 2

- **Rt. tinnitus with sudden sensorineural hearing loss**
- 35 y/o female
- She suddenly had rt. hearing loss with severe tinnitus. She had been diagnosed and treated as depression.
- Although her hearing loss was markedly improved by steroid treatment, she died from suicide because of her disabled tinnitus.
Peripheral theory of tinnitus

1. Valiability of tinnitus
2. Tinnitus after vestibular or cochlear neurectomy
3. Tinnitus masking
4. Tinnitus without hearing loss

Tinnitus after cochlear neurectomy

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dis appeared</td>
<td>25</td>
</tr>
<tr>
<td>Improvement</td>
<td>36</td>
</tr>
<tr>
<td>Unchanged</td>
<td>32</td>
</tr>
<tr>
<td>Deterioration</td>
<td>7</td>
</tr>
</tbody>
</table>
Tinnitus distress model (Keio model: Central theory)

Distress network

- Depression
- Anxiety
- Attention
- Cognition
- Memory
- Auditory cortex
- Thalamus
- Auditory pathway
- Cochlea
- Non-auditory brain

CN
1. Auditory abnormal sensation

2. Evaluation

3. Central management
## THI
(Tinnitus handicap inventory)

**Identify difficulties caused by tinnitus**

<table>
<thead>
<tr>
<th>Please answer every question.</th>
<th>Yes</th>
<th>Sometimes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Because of your tinnitus, is it difficult for you to concentrate?</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>4</strong> Does your tinnitus make you feel confused?</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>12</strong> Does your tinnitus make it difficult for you to enjoy life?</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>16</strong> Does your tinnitus make you upset?</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>25</strong> Does your tinnitus make you feel insecure?</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Grade

- **Slight** (0~16)
- **Moderate** (18~56)
- **Severe** (58~100)
40% of severe THI patients have depression

SDS: Self-depression scale (Questionnaires of depression)

n=1424
r=0.571 (p<0.0001)

40% of severe THI patients have depression
80% of severe THI patients have high anxiety

STAI: State-Trait Anxiety Index (Questionnaire of anxiety)

\[ n=1426 \]
\[ r=0.580 \quad (p<0.0001) \]

80% of severe THI patients have high anxiety.
THI vs Insomnia

\[ n=574 \]
\[ r=0.485 \ (p<0.0001) \]

- THI grade
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- THI score
  - 0
  - 5
  - 10
  - 15
  - 20

- PSQI score
  - 0
  - 5
  - 10
  - 15
  - 20

Number of patients

- Slight
- Moderate
- Severe

Insomnis-  Insomnia+

Insomnis-  Insomnia+
**Novel standard tinnitus test**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td><strong>TSCHQ</strong></td>
</tr>
<tr>
<td>2</td>
<td>Subjective evaluations</td>
</tr>
<tr>
<td>3</td>
<td>Pitch match test, Loudness balance test</td>
</tr>
<tr>
<td>4</td>
<td><strong>THI</strong></td>
</tr>
<tr>
<td>5</td>
<td><strong>SDS</strong> (depression), <strong>STAI</strong> (anxiety), <strong>PSQI</strong> (sleep)</td>
</tr>
<tr>
<td>6</td>
<td>VAS (loudness • annoyance • duration)</td>
</tr>
</tbody>
</table>
EEG in FP1

FP1 (prefrontal area): EEG may reflect anxiety.

1. Portable EEG device
2. EEG pattern
3. Tinnitus group n=15, Control group n=10
Tinnitus may be related to 9~10Hz peak pattern

Sensitivity: 84%, Specificity: 80%
Cochlear autonomic reflex

Normal subject exogenous noise

Unpleasant sound

Tinnitus patients endogenous noise

Unpleasant noise: Band noise (BN) centered at 500Hz, discomfort level +10 dBHL
Tinnitus-mimicking noise reduces fingertip temperature in tinnitus patients

Tinnitus-mimicking noise+10dB SPL (average 6300Hz)

Tinnitus patients (n=6, average THI 52)

Comfortable noise: 500Hz BN MCL

Uncomfortable noise: 500Hz BN UCL+10dB

Tinnitus-mimicking noise: Pitch, loudness+10dB SPL
BDNF as a biomarker of tinnitus

BDNF may be related to annoyance of tinnitus, and be a candidate for biomarker of tinnitus.

![Graph showing the relationship between Plasma BDNF (pg/mL) and THI score]

- **r = -0.36**
- **p = 0.016**
- **n = 42**
### Tinnitus related gene analysis

#### Large individual difference in tinnitus perception and annoyance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr</th>
<th>SNP ID</th>
<th>Genotypes</th>
<th>reported Minor allele</th>
<th>JPT (allele frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR</td>
<td>22</td>
<td>rs140504</td>
<td>GG/GA/AA</td>
<td>G</td>
<td>0.500/0.500$</td>
</tr>
<tr>
<td>BCR</td>
<td>22</td>
<td>rs131690</td>
<td>GG/GA/AA</td>
<td>G</td>
<td>0.765/0.235$</td>
</tr>
<tr>
<td>BCR</td>
<td>22</td>
<td>rs131702</td>
<td>GG/GT/TT</td>
<td>G</td>
<td>0.593/0.407$</td>
</tr>
<tr>
<td>SLC6A15</td>
<td>12</td>
<td>rs1545843</td>
<td>AA/AG/GG</td>
<td>A</td>
<td>0.633/0.367$</td>
</tr>
<tr>
<td>ADCYAP1R1</td>
<td>7</td>
<td>rs2267735</td>
<td>GG/GC/CC</td>
<td>C</td>
<td>0.521/0.479$</td>
</tr>
<tr>
<td>SIRT1</td>
<td>10</td>
<td>rs10997870</td>
<td>TT/TG/GG</td>
<td>T</td>
<td>0.851/0.149$</td>
</tr>
<tr>
<td>HTR2A</td>
<td>13</td>
<td>rs7997012</td>
<td>AA/AG/GG</td>
<td>A</td>
<td>0.827/0.173#</td>
</tr>
<tr>
<td>MAOB (male)</td>
<td>X</td>
<td>rs1799836</td>
<td>CC/CT/TT</td>
<td>C</td>
<td>0.853/0.147*</td>
</tr>
<tr>
<td>MAOB (female)</td>
<td>X</td>
<td>rs1799836</td>
<td>CC/CT/TT</td>
<td>C</td>
<td>0.853/0.147*</td>
</tr>
<tr>
<td>MAOB (sex unknown)</td>
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<td></td>
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<td></td>
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</tbody>
</table>

BCR: Breakpoint cluster region, SLC6A15: Solute carrier family 6 (neurotransmitter transporter), member 15, ADCYAP1R1: Pituitary adenylate cyclase-activating polypeptide receptor, type 1, SIRT1: Sirtuin 1, HTR2A: 5-hydroxytryptamine receptor 2A, MAOB: monoamine oxidative B
### SNP analysis

<table>
<thead>
<tr>
<th>Gene polymorphisms</th>
<th>Allele</th>
<th>Mild to moderate</th>
<th>Severe</th>
<th>Total</th>
<th>P for Fisher's test</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td><strong>BCR</strong> rs140504</td>
<td>A allele</td>
<td>92(57.5)</td>
<td>49(45.4)</td>
<td>141(52.6)</td>
<td>0.061</td>
<td>1.629</td>
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<tr>
<td></td>
<td>G allele</td>
<td>68(42.5)</td>
<td>59(54.6)</td>
<td>127(47.4)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>108</td>
<td>268</td>
<td></td>
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<tr>
<td><strong>BCR</strong> rs131690</td>
<td>A allele</td>
<td>123(76.9)</td>
<td>79(73.1)</td>
<td>202(75.4)</td>
<td>0.563</td>
<td>1.220</td>
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<td></td>
<td>G allele</td>
<td>37(23.1)</td>
<td>29(26.9)</td>
<td>66(24.6)</td>
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<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>108</td>
<td>268</td>
<td></td>
<td></td>
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<tr>
<td><strong>BCR</strong> rs131702</td>
<td>G allele</td>
<td>53(33.1)</td>
<td>53(50)</td>
<td>106(39.8)</td>
<td>0.007</td>
<td>2.019</td>
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<td></td>
<td>T allele</td>
<td>107(66.9)</td>
<td>53(50)</td>
<td>160(60.2)</td>
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<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>106</td>
<td>266</td>
<td></td>
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<tr>
<td><strong>SLC6A15</strong> rs1545843</td>
<td>G allele</td>
<td>107(66.9)</td>
<td>67(62)</td>
<td>174(67.9)</td>
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<td>1.235</td>
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<td>Total</td>
<td>160</td>
<td>108</td>
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<td></td>
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<tr>
<td><strong>ADCYAP1R1</strong> rs2267735</td>
<td>C allele</td>
<td>81(50.6)</td>
<td>48(44.4)</td>
<td>129(48.1)</td>
<td>0.383</td>
<td>0.780</td>
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<tr>
<td></td>
<td>G allele</td>
<td>79(49.4)</td>
<td>60(55.6)</td>
<td>139(51.9)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>108</td>
<td>268</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SIRT1</strong> rs10997870</td>
<td>G allele</td>
<td>131(81.9)</td>
<td>87(80.6)</td>
<td>218(81.3)</td>
<td>0.873</td>
<td>1.353</td>
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<tr>
<td></td>
<td>T allele</td>
<td>29(18.1)</td>
<td>21(19.4)</td>
<td>50(18.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>108</td>
<td>268</td>
<td></td>
<td></td>
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<tr>
<td><strong>HTR2A</strong> rs7997012</td>
<td>A allele</td>
<td>32(20)</td>
<td>25(23.1)</td>
<td>57(21.3)</td>
<td>0.546</td>
<td>1.205</td>
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<tr>
<td></td>
<td>G allele</td>
<td>128(80)</td>
<td>83(76.9)</td>
<td>211(78.7)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>160</td>
<td>108</td>
<td>268</td>
<td></td>
<td></td>
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<tr>
<td><strong>MAOB (male)</strong> rs1799836</td>
<td>C allele</td>
<td>4(12.1)</td>
<td>3(13)</td>
<td>7(12.5)</td>
<td>1.000</td>
<td>1.088</td>
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<td>T allele</td>
<td>29(87.9)</td>
<td>20(87)</td>
<td>49(87.5)</td>
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<tr>
<td></td>
<td>Total</td>
<td>33</td>
<td>23</td>
<td>56</td>
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<tr>
<td><strong>MAOB (female)</strong> rs1799836</td>
<td>C allele</td>
<td>19(22.1)</td>
<td>8(13.3)</td>
<td>27(18.5)</td>
<td>0.201</td>
<td>0.543</td>
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<tr>
<td></td>
<td>T allele</td>
<td>67(77.9)</td>
<td>52(86.7)</td>
<td>119(81.5)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Total</td>
<td>86</td>
<td>60</td>
<td>146</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Resting-state fMRI data analysis

$\beta = \frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right)$

BOLD in BA42L

Fisher transformation

$\beta$-value: 1.25

Correlation coefficient ($\gamma$): 0.85

Conn toolbox v.13
Functional connectivity (FC) in resting-state fMRI

Normal subject (36 years old)

$\beta$ value between left and right auditory cortex: 1.25

Strong FC between left and right auditory cortex

BOLD in BA42L

BOLD in BA42R
Auditory-based functional connectivity

Control (n=10)  Tinnitus (n=9)  
(p<0.01)
1. Auditory abnormal sensation
2. Evaluation
3. Central management
Tinnitus treatment

Treatment for tinnitus

- Drug therapy
- Surgical therapy: cochlear neurectomy
- rTMS•tDCS

Treatment for tinnitus annoyance

Habituation therapy

- Drug therapy: antidepressants, sleep medicines
- Psychotherapy: cognitive-behavioral therapy
- TRT: directive counseling + sound therapy
Auditory pathway has an abundance of serotonin receptors.

<table>
<thead>
<tr>
<th>Distress network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve directly “depression and anxiety” of distress network → Improve distress</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI)</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitor (SNRI)</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressant (NaSSA)</td>
</tr>
</tbody>
</table>
Patients with depression and anxiety showed better improvement

**Paroxetine:**
10~20mg/d, 6 months

Oishi et al. 2010

**SSRI outcome**

THI

<table>
<thead>
<tr>
<th>THI score</th>
<th>Depression &amp; anxiety</th>
<th>Anxiety alone</th>
<th>No anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**VAS (loudness)**

<table>
<thead>
<tr>
<th>Loudness of tinnitus</th>
<th>Depression &amp; anxiety</th>
<th>Anxiety alone</th>
<th>No anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p<0.01, *: p<0.05**
Attention
Cognition
Depression.
Anxiety

Non-auditory brain

TRT
directive
counseling

Attention.
Cognition

Auditory cortex
Thalamus
Memory

Auditory pathway

Cochlea

Sound therapy
Treatment effects of SG

Treated with SG only for more than 1 year (n=95)

- Loudness of tinnitus:
  - Slightly improved: 31%
  - No change: 58%
  - Worsening: 8%
  - Remarkable improvement: 3%

- Distress of tinnitus:
  - Slightly improved: 58%
  - No change: 25%
  - Worsening: 7%
  - Remarkable improvement: 10%

**p<0.01  *p<0.05

Oishi et al. 2013
Treatment effect of HA

**Loudness of tinnitus**

- SG: 34%
- HA: 92%

**Distress of tinnitus**

- SG: 68%
- HA: 95%

- Worse
- No change
- Slightly improved
- Remarkable improve
- Disappearance

Rate of improvement: slightly improved
Why is sound therapy with HA effective?

**Distress network**
- Relative reduction of tinnitus → improve distress
- Improve hearing impairment → improve QOL
- Change attention target tone induced by HA → speech discrimination → positive emotional effects

**Auditory pathway**
- Normalization of neural activity of auditory pathway
- Rich sounds induce relative reduction of tinnitus tone
Sound therapy with HA restores the FC changes

80 years old male
Right tinnitus

Before HA
- THI 64
- SDS 49
- STAI state 65
- trait 54

After HA
- THI 20
- SDS 27
- STAI state 36
- trait 41

β-value between left and right auditory cortex

Anterior cingulate gyrus

THI 64
SDS 49
STAI state 65
trait 54

THI 20
SDS 27
STAI state 36
trait 41
Multimodality treatment

slight (Grade 1): THI < 18

moderate (Grade 2): THI < 56

Drug therapy

Sound therapy (CD, radio etc.)

severe (Grade 3): THI > 58

Drug therapy

Sound therapy (SG, HA etc.)

severe (Grade 4): depression

Drug therapy

Sound therapy (SG, HA etc.)

psychotherapy

Follow-up

3 mo

6 mo

12 mo
A method of non-invasive stimulating the brain through the intact scalp by law of electromagnetic induction.

Single pulse: produce complex but short responses.
Repeated pulse: more prolonged effects on the brain

High frequency (5-20Hz):
- increase cortical excitability

Low frequency (≤1Hz):
- decrease cortical excitability

Tinnitus treatment

(Magstim Rapid)
Effect of rTMS

Stimulation protocol

- **Intensity**: 110% of individual resting motor threshold
- **Coil position**: left auditory cortex
- **Frequency**: low frequency (1Hz)
- **Number of pulses**: 1200 stimulations (20 min)
- **Number of sessions**: 10 sessions

**THI (n=9)**

- Effects of rTMS continued until 6 month later
rTMS induces c-Fos expression in auditory cortex

rTMS induce plasticity of auditory cortex
tDCS
Transcranial direct current stimulation

**Basis**
- A non-invasive procedure of cortical stimulation.
- **Anodal** tDCS has an excitatory effect on the underlying cerebral cortex by depolarizing neurons.
- **Cathodal** tDCS decreases cortical excitability by inducing hyperpolarization.

**Protocol**
- **Device**: DC-Stimulator (NeuroConn)
- Cathode was placed over the **left** primary auditory cortex.
- Anode was placed over the **right** primary auditory cortex.
- **Intensity**: 1mA, **Duration**: 10 min
Change of fMRI after tDCS

61 y/o male

β value (tDCS responders)

Before tDCS

After tDCS

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

B A 41

B A 42
Central management

Depression
Anxiety

Attention
Cognition

Non-auditory brain
Directive counseling
Psychotherapy
Drug therapy

Auditory cortex
Thalamus

Memory

Auditory pathway
CN

Sound therapy

Cochlea

rTMS
tDCS