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Current Trend of Treatment of Tinnitus and Hyperacusis

IFOS World Course, 2019

Dept. f Otolaryngology
Keio University
Kaoru Ogawa MD, PhD

1 **Auditory abnormal sensation**

2 Evaluation

3 Central management

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Abnormal sensations

Audition	Vison
tinnitus	floaters
hyperacusis	photopsia
autophony	
phonophobia	photophobia
ear fullness	blurred vision
paracusis	metamorphopsia
diplacusis	
diplacusis loci	
auditory illusion	visual illusion

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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 (1.5million) have tinnitus with severe annoyance.
The German Tinnitus League (1999)
1/4 of the total population (30 million) experienced tinnitus.
Japanese Health and Welfare (2006)

＝ 20%（24 million）
＝ 3%（3~4million）

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Hyperacusis

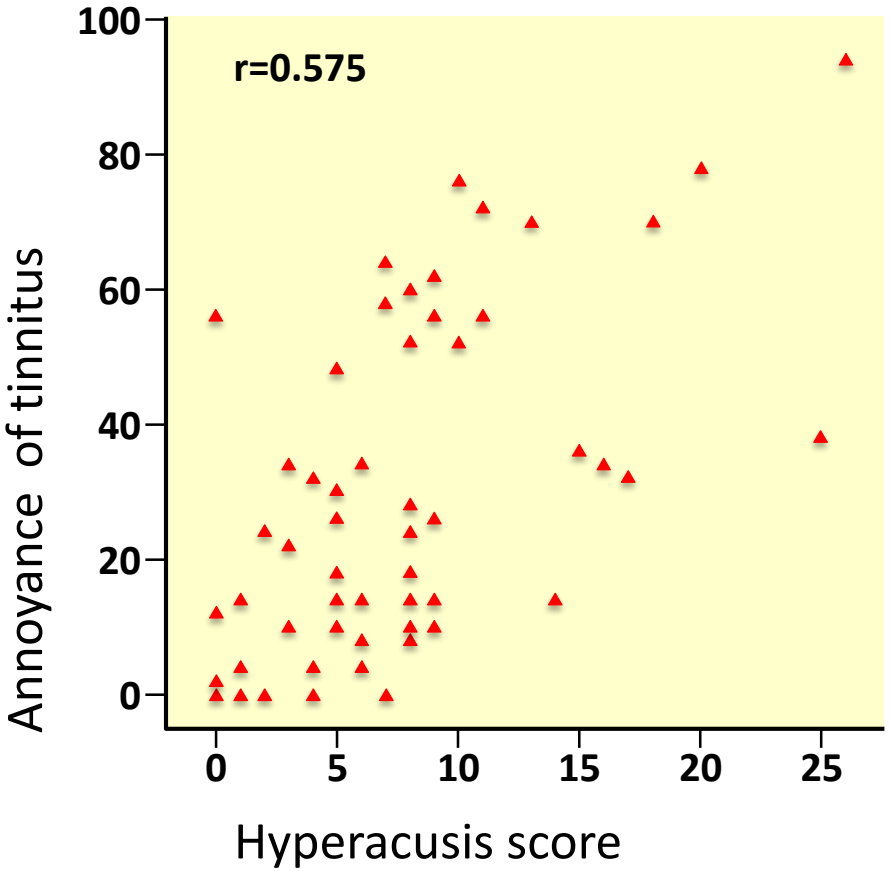
Definition

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

（Steadman's Medical Dictionary）

- **sensitive hearing**
- **decreased sound tolerance**
- **phono**phobia
- misophonia

- Hyperacusu: **20～45% of Tinnitus**
- **Tinnitus: 80～90% of Hyperacusis**



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Difficulity 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%

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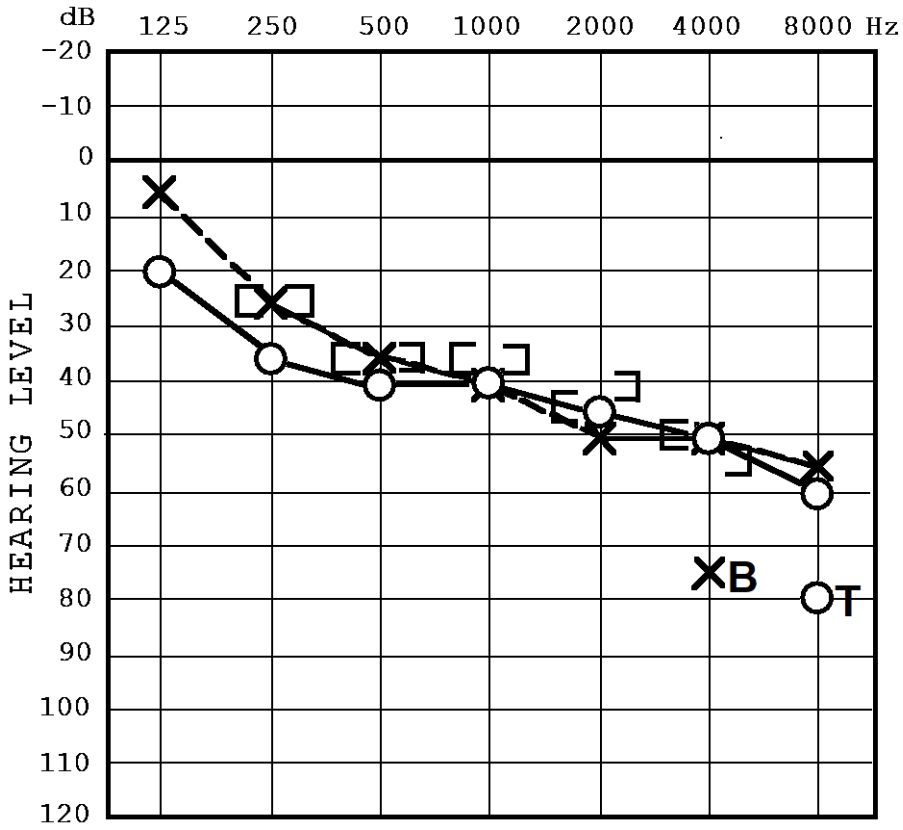
Tinnitus: Case 1

- **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**



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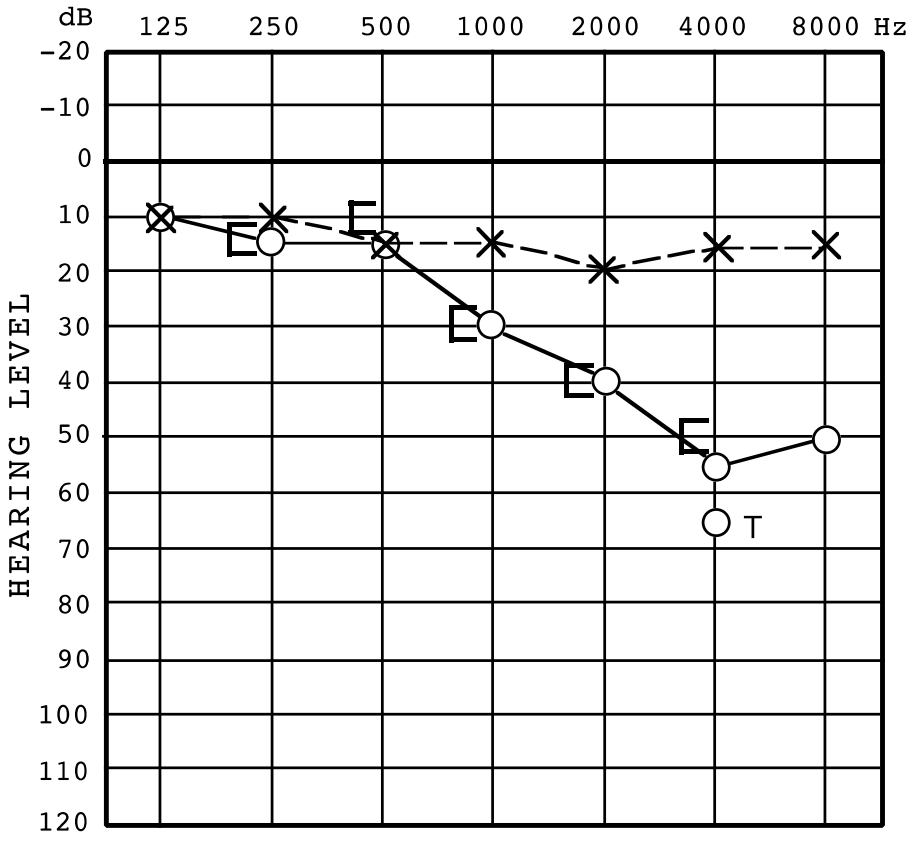
Tinnitus: Case 2

- **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.**



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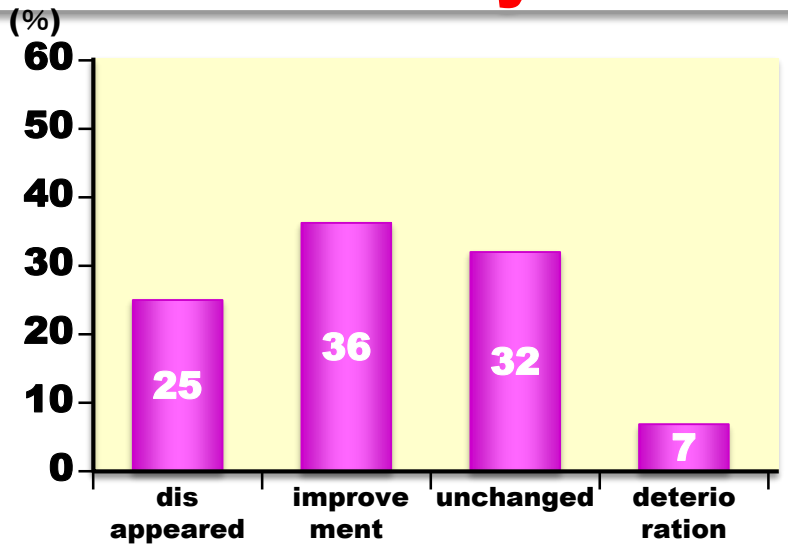
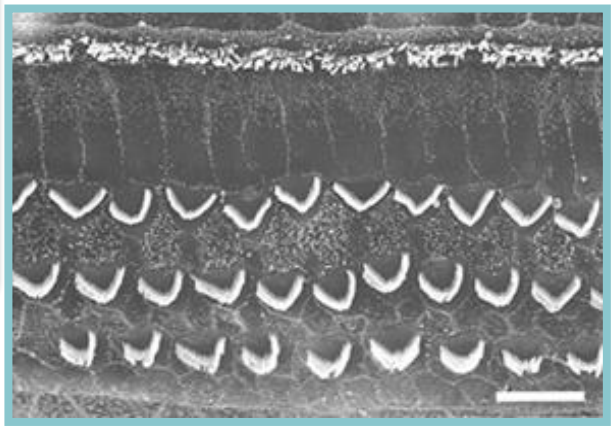
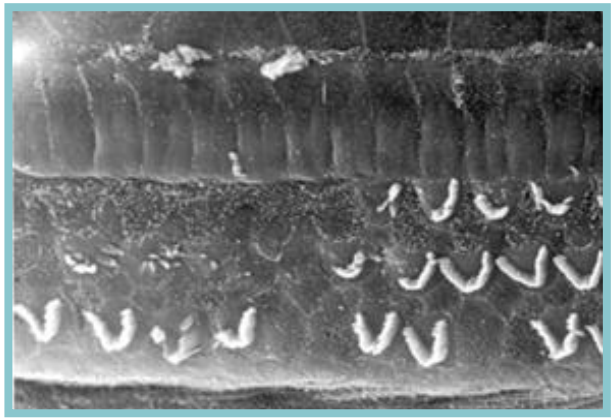
Peripheral theory of tinnitus

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

Tinnitus after cochlear neurectomy







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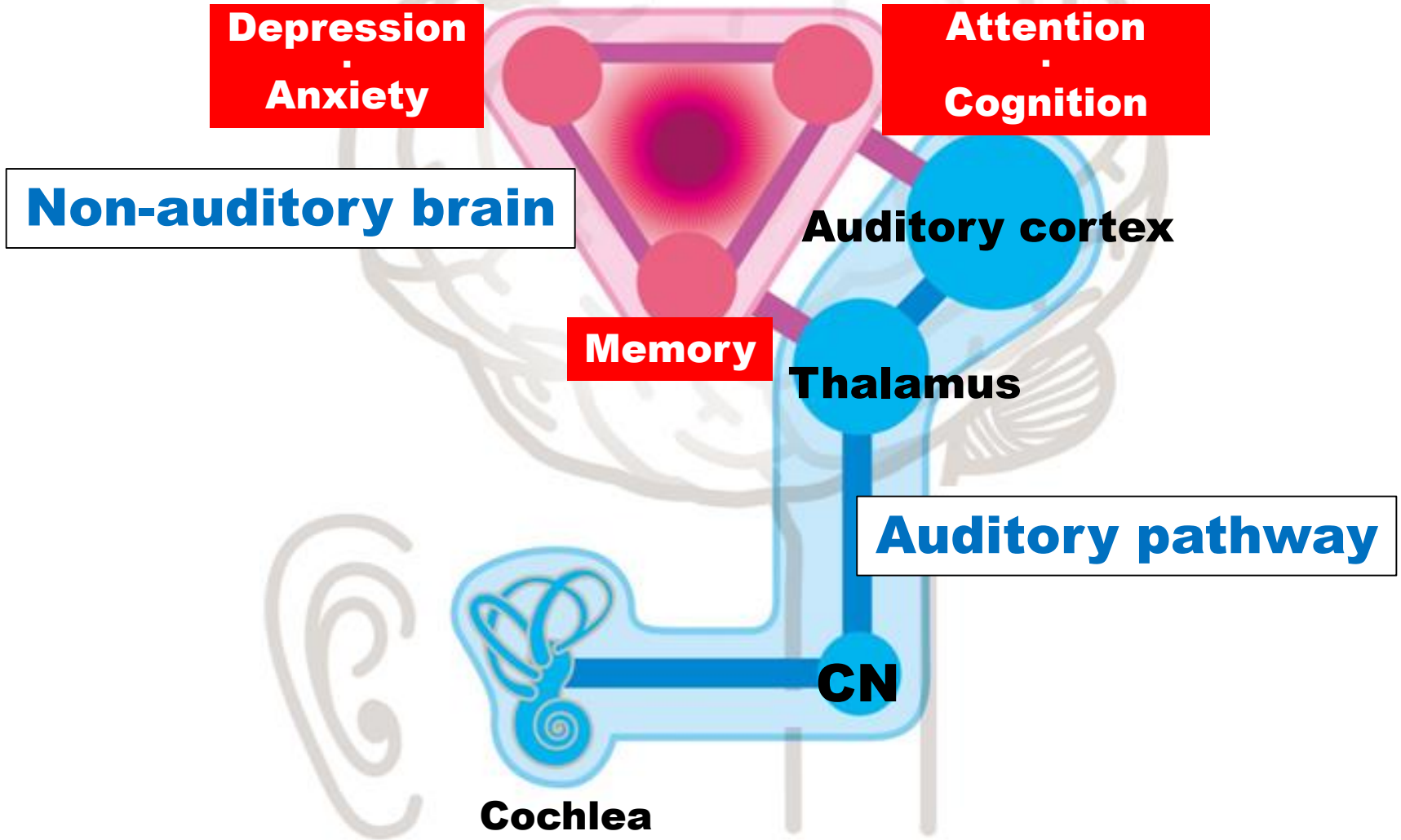
Tinnitus distress model (Keio model: Central theory)

Distress network



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THI

(Tinnitus handicap inventory)

Identify difficulties caused by tinnitus

Please answer every question.		Yes	Sometimes	No
1	Because of your tinnitus, is it difficult for you to concentrate?	4	2	0
4	Does your tinnitus make you feel confused?	4	2	0
12	Does your tinnitus make it difficult for you to enjoy life?	4	2	0
16	Does your tinnitus make you upset?	4	2	0
25	Does your tinnitus make you feel insecure?	4	2	0

Grade

Slight (0~16)	Moderate (18~56)	Severe (58~100)

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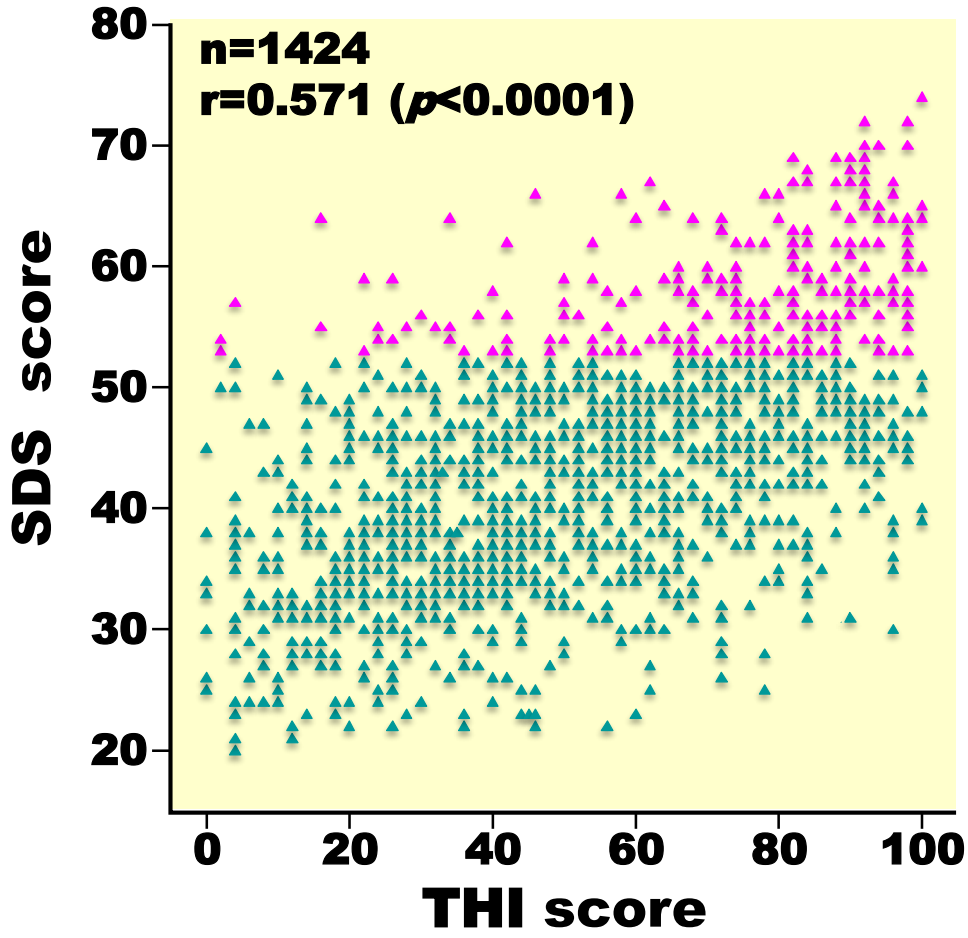
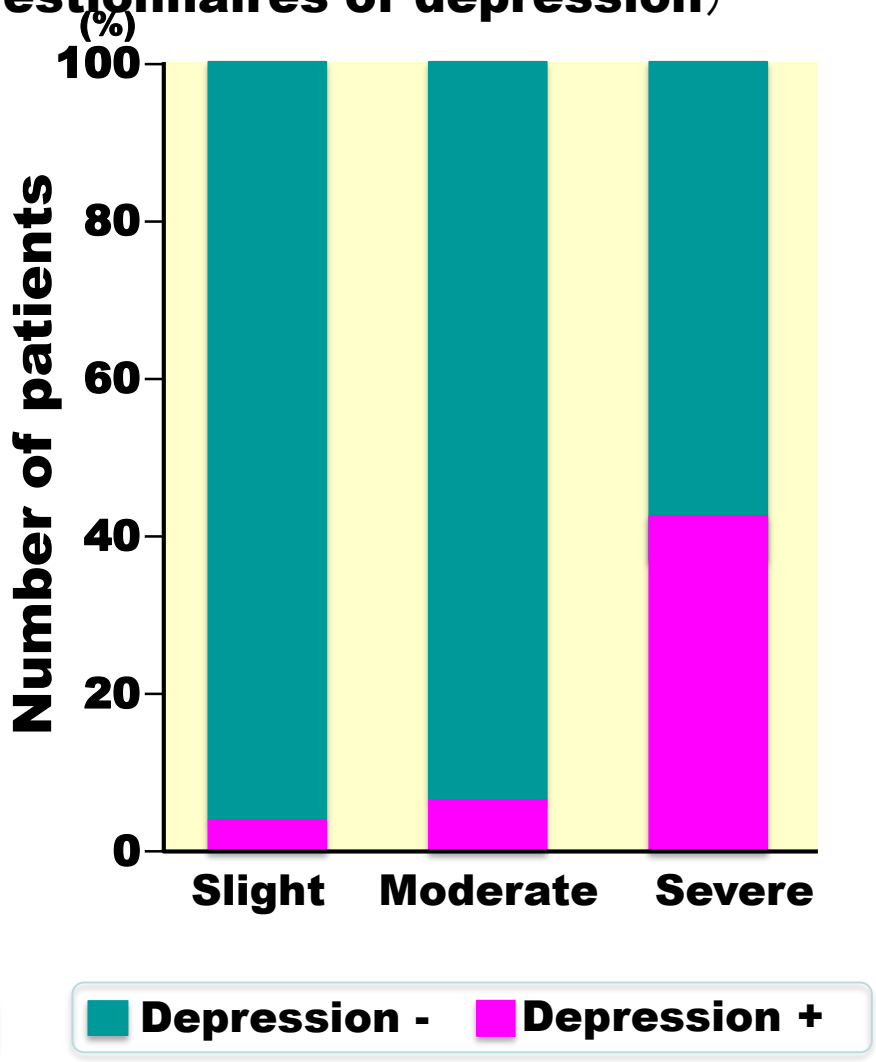
40% of severe THI patients have depression

SDS: Self-depression scale （Questionnaires of depression）





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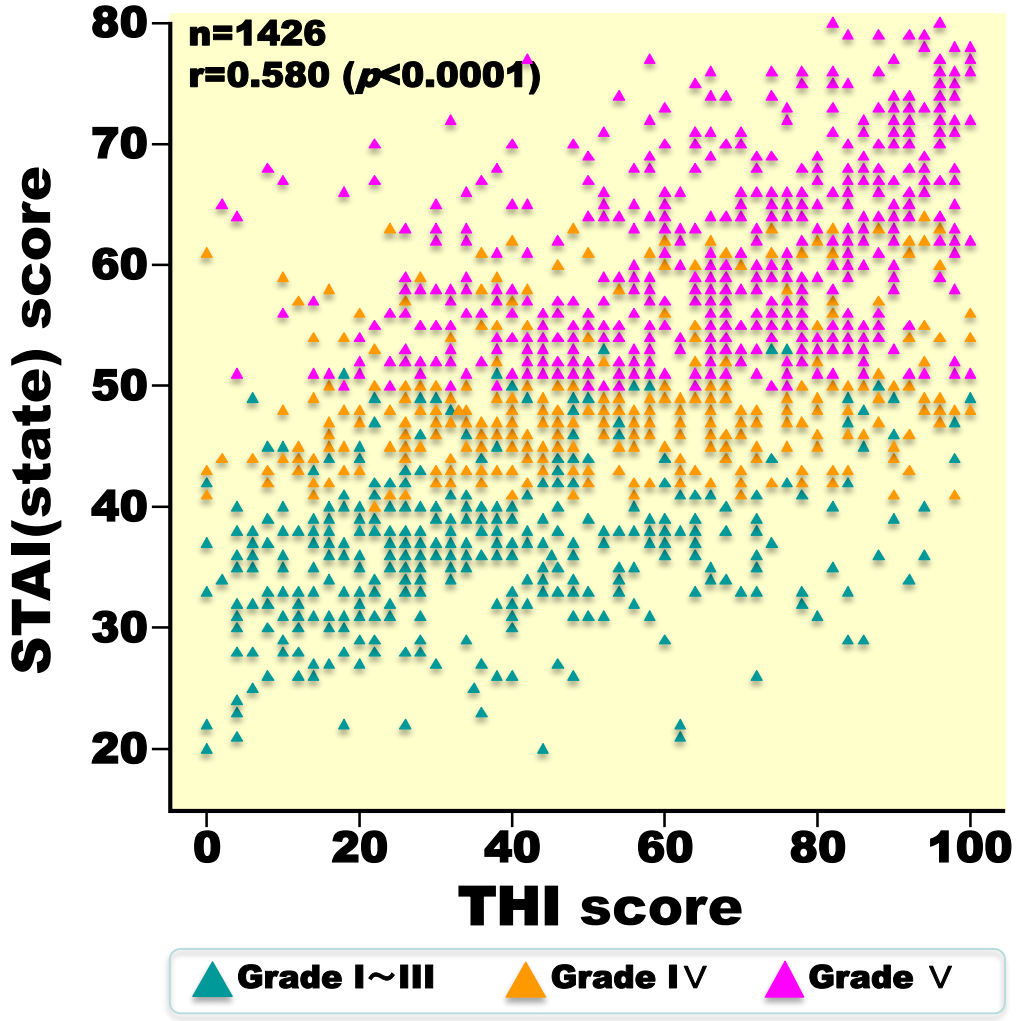
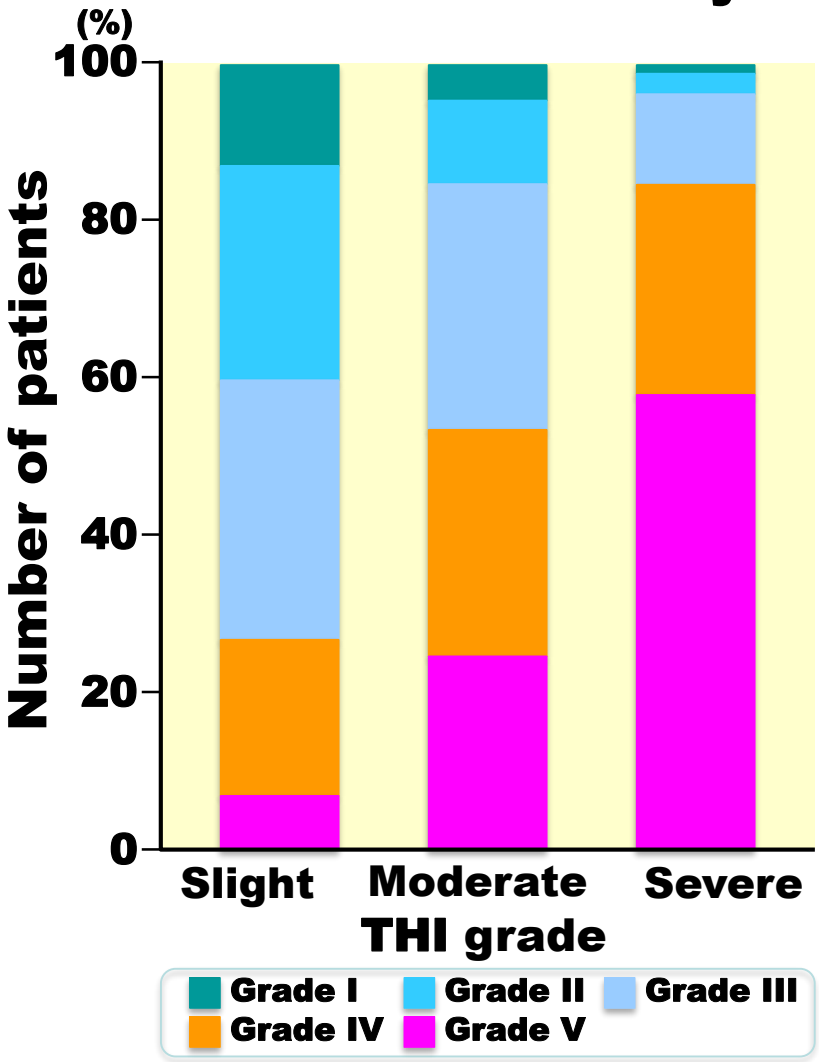
80% of severe THI patients have high anxiety

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





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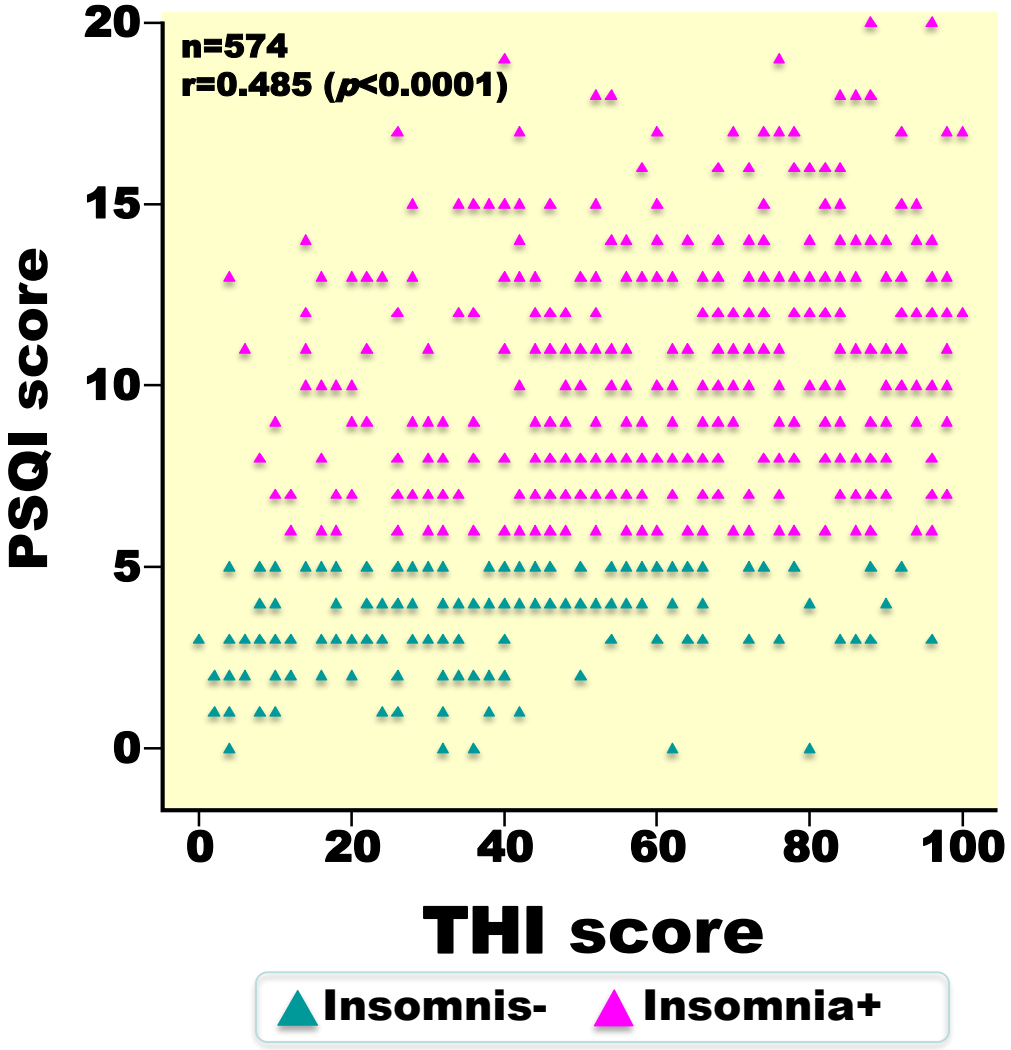
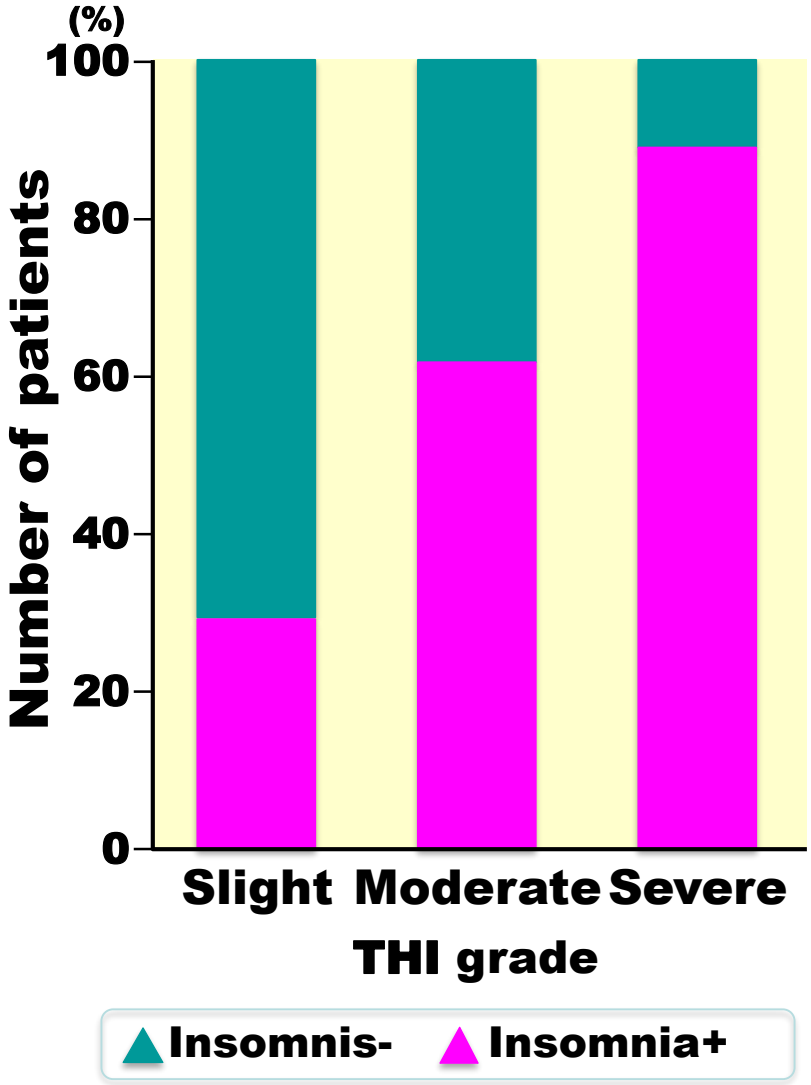
THI vs Insomnia





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Novel standard tinnitus test

1. **TSCHQ**
2. Subjective evaluations
3. Pitch match test, Loudness balance test
4. **THI**
5. **SDS** (depression), **STAI** (anxiety), **PSQI** (sleep)
6. VAS (loudness・annoyance・duration)

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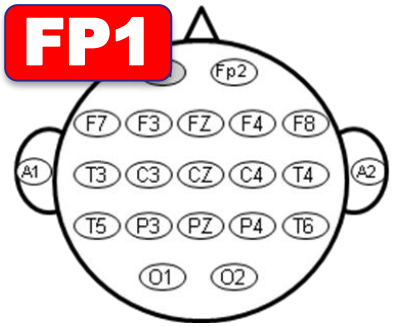
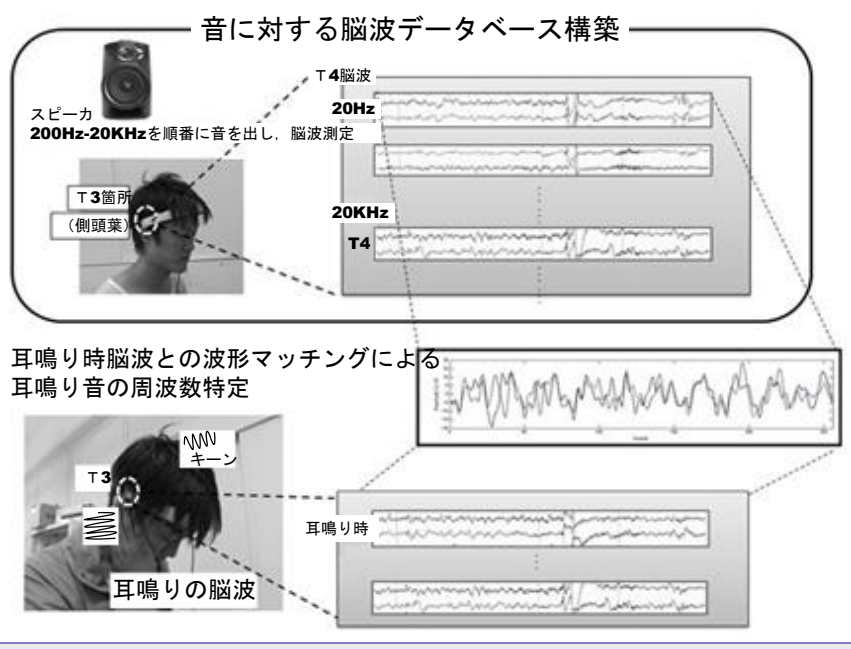
EEG in FP1

●FP1（prefrontal area）: EEG may reflect anxiety.



1. **Portable EEG device**
2. **EEG pattern**
3. **Tinnitus group n=15，Control group n=10**



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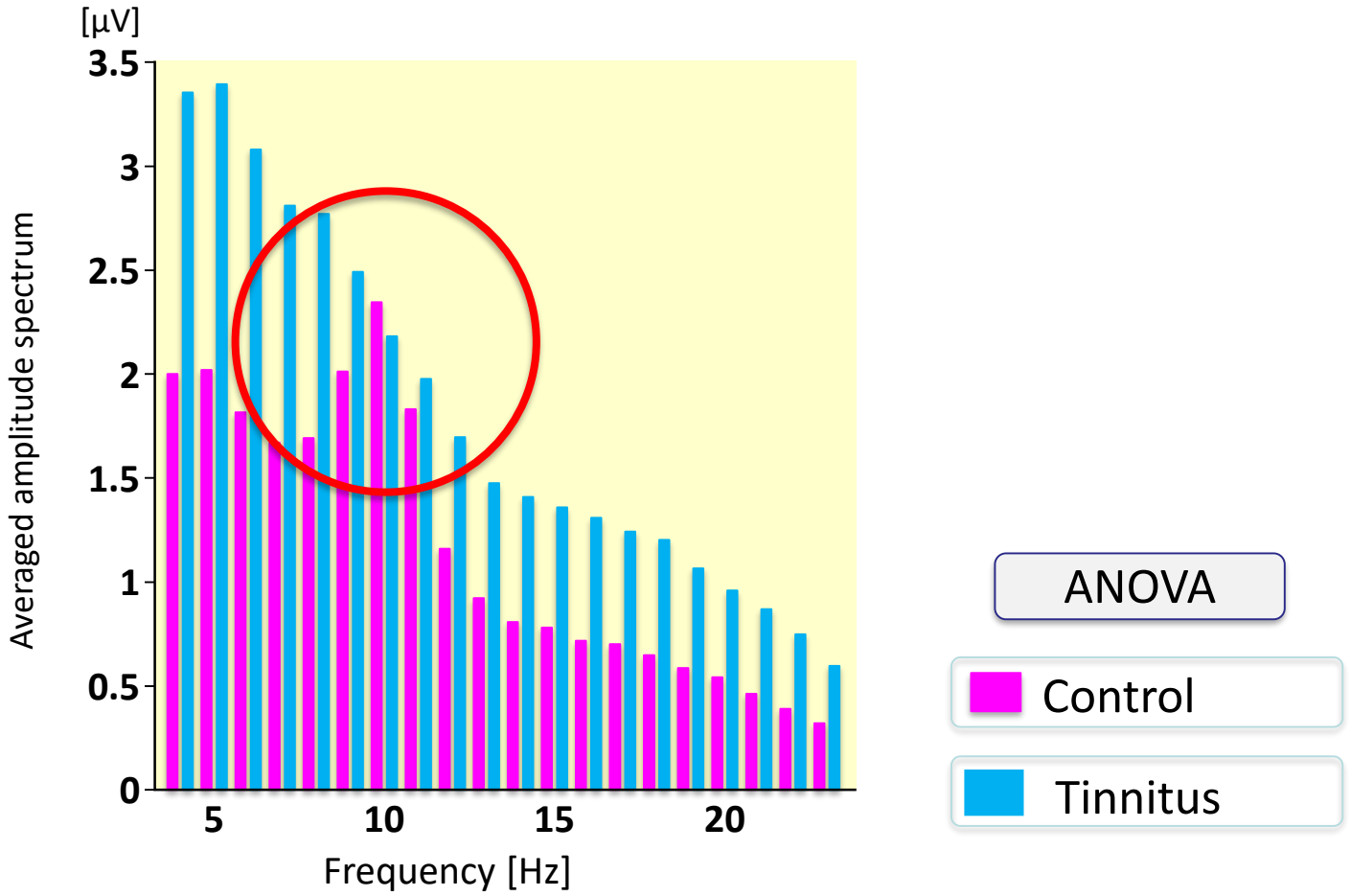
Tinnitus may be related to 9~10Hz peak pattern

Sensitivity: 84%, Specificity: 80%



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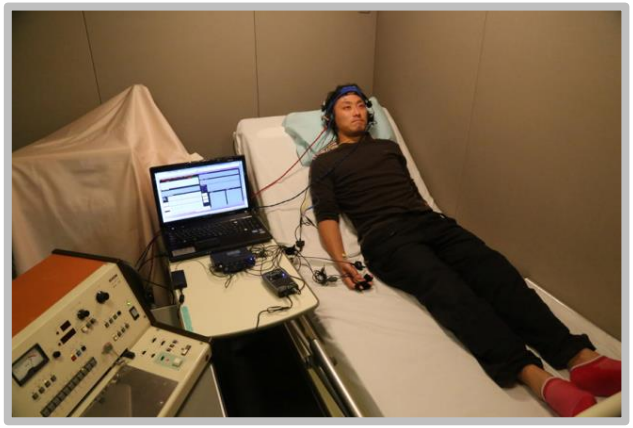
Cochlear autonomic reflex

Unpleasant sound

Normal subject
exogenous noise → **Autonomic reflex**

Tinnitus patients
endogenous noise → **?**

Unplreasant noise : Band noise (BN) centered at 500Hz, discomfort level+10 dBHL



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Tinnitus-mimicking noise reduces fingertip temperature in tinnitus patients

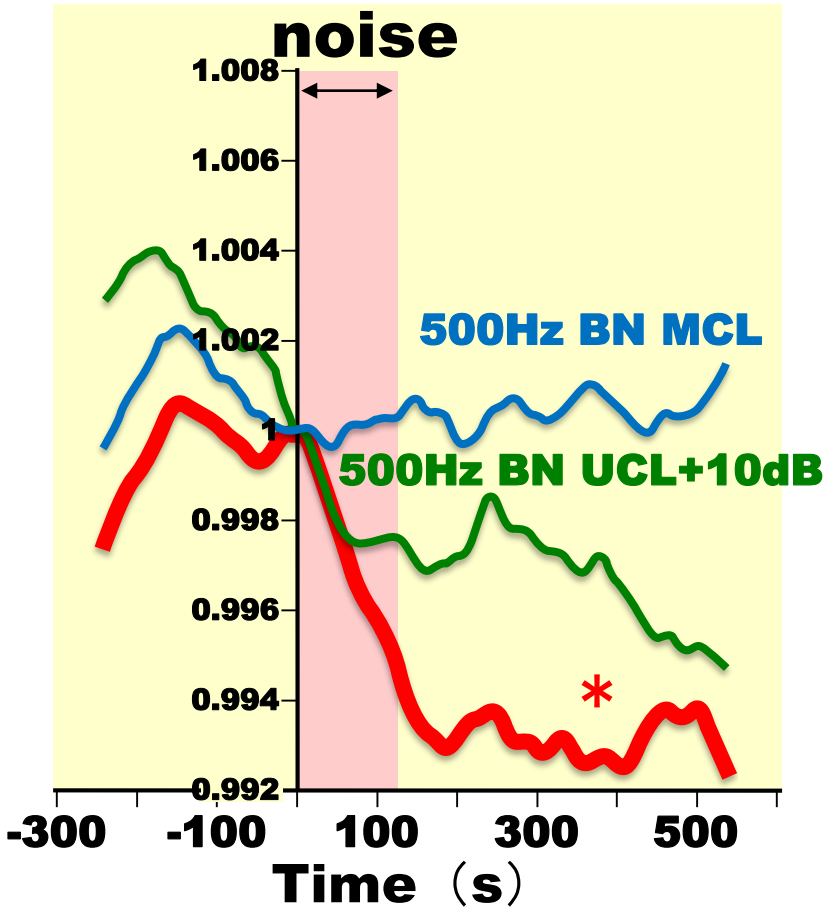
Tinnitus-mimicking noise+10dB SPL (average 6300Hz)

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



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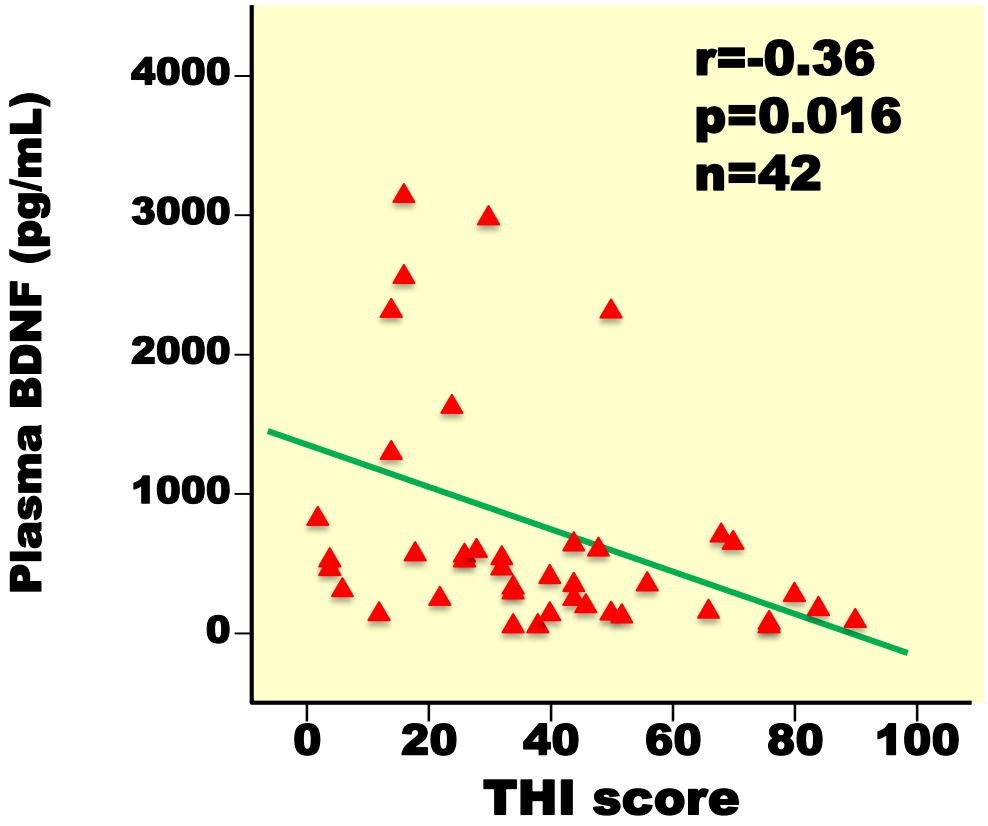
BDNF as a biomarker of tinnitus

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



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Tinnitus related gene analysis

Large individual difference in tinnitus perception and annoyance

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

BCR: Breakpoint cluster region , SLC6A15: Solute carrier family 6 (neurotransmitter transporter), member 15, ADCYAP1R1: Pituitary adenylate cyclase-activating polypeptide receptor, type1, SIRT1: Sirtuin 1, HTR2A: 5-hydroxytryptamine receptor 2A, *MAOB: monoamine oxidative B*

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SNP analysis

Gene polymorphisms		Allele	All Subjects (n = 134) Mild to moderate	Severe	Total	*P for Fisher's test*	Odds Ratio
BCR	rs140504	A allele	92(57.5)	49(45.4)	141(52.6)	0.061	1.629 (0.996-2.664)
		G allele	68(42.5)	59(54.6)	127(47.4)		
		Total	160	108	268		
BCR	rs131690	A allele	123(76.9)	79(73.1)	202(75.4)	0.563	1.220 (0.695-2.141)
		G allele	37(23.1)	29(26.9)	66(24.6)		
		Total	160	108	268		
BCR	rs131702	G allele	53(33.1)	53(50)	106(39.8)	0.007	2.019 (1.220-3.340)
		T allele	107(66.9)	53(50)	160(60.2)		
		Total	160	106	266		
SLC6A15	rs1545843	A allele	53(33.1)	41(38)	94(35.1)	0.436	1.235 (0.742-2.056)
		G allele	107(66.9)	67(62)	174(67.9)		
		Total	160	108	268		
ADCYAP1R1	rs2267735	C allele	81(50.6)	48(44.4)	129(48.1)	0.383	0.780 (0.478-1.274)
		G allele	79(49.4)	60(55.6)	139(51.9)		
		Total	160	108	268		
SIRT1	rs10997870	G allele	131(81.9)	87(80.6)	218(81.3)	0.873	1.353 (0.659-2.780)
		T allele	29(18.1)	21(19.4)	50(18.7)		
		Total	160	108	268		
HTR2A	rs7997012	A allele	32(20)	25(23.1)	57(21.3)	0.546	1.205 (0.667-2.177)
		G allele	128(80)	83(76.9)	211(78.7)		
		Total	160	108	268		
MAOB (male)	rs1799836	C allele	4(12.1)	3(13)	7(12.5)	1.000	1.088 (0.219-5.395)
		T allele	29(87.9)	20(87)	49(87.5)		
		Total	33	23	56		
MAOB (female)	rs1799836	C allele	19(22.1)	8(13.3)	27(18.5)	0.201	0.543 (0.220-1.337)
		T allele	67(77.9)	52(86.7)	119(81.5)		
		Total	86	60	146		

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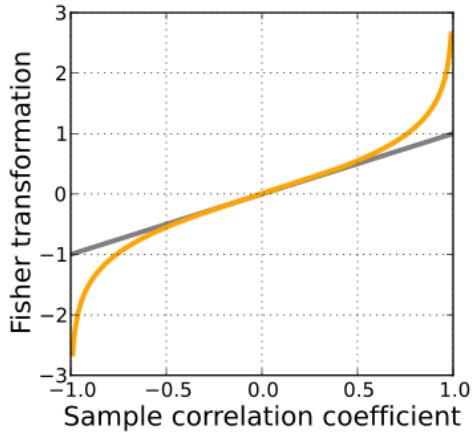
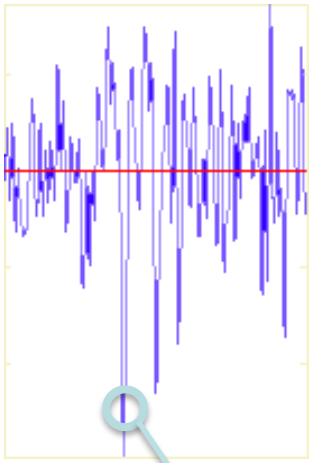
Resting-state fMRI data analysis

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



BOLD in BA42L



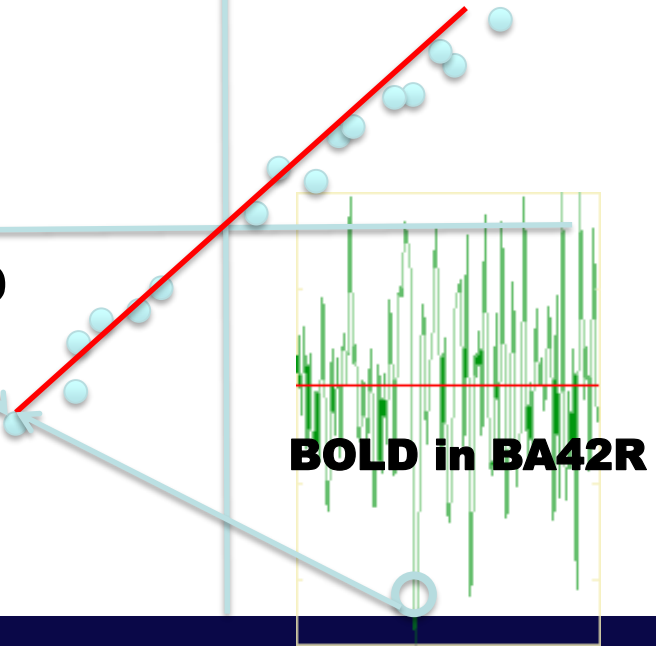
42L BOLD

Fisher transformation

Correlation coefficient（γ）：0.85

βvalue：1.25

42R BOLD



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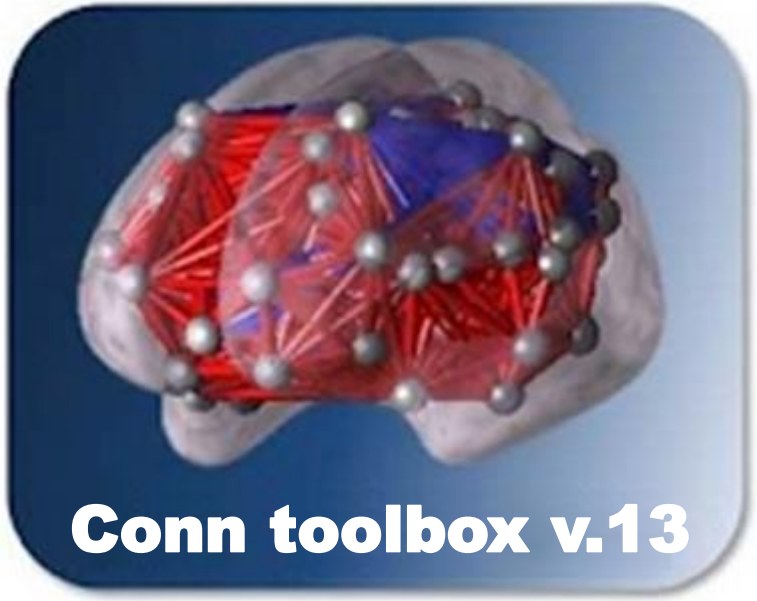

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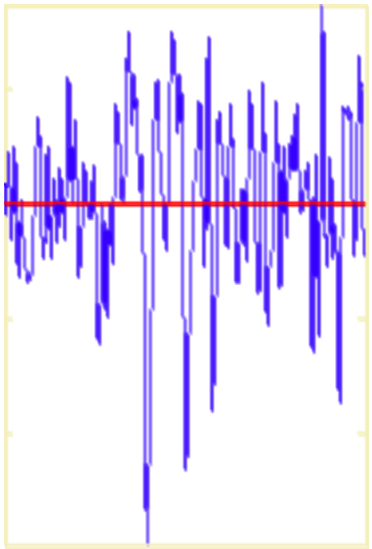
Functional connectivity (FC) in resting-state fMRI

Normal subject (36 years old)

β value between left and right auditory cortex : 1.25



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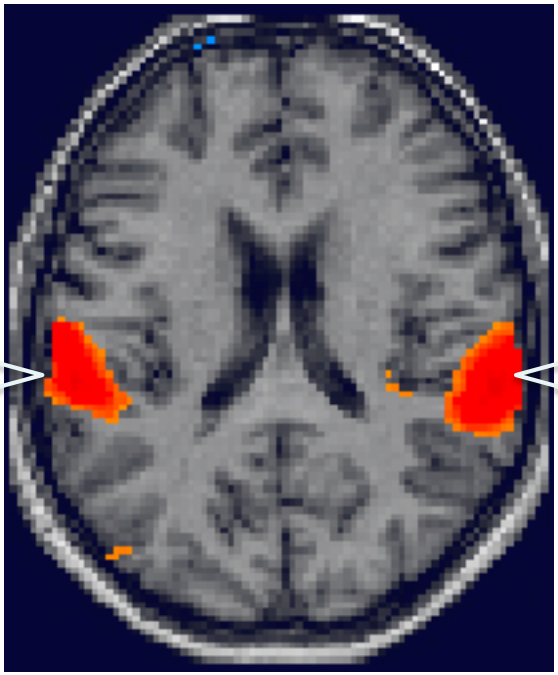

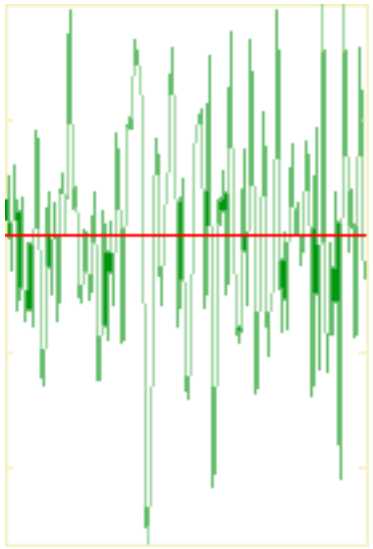

BOLD in BA42R

Strong FC between left and right auditory cortex

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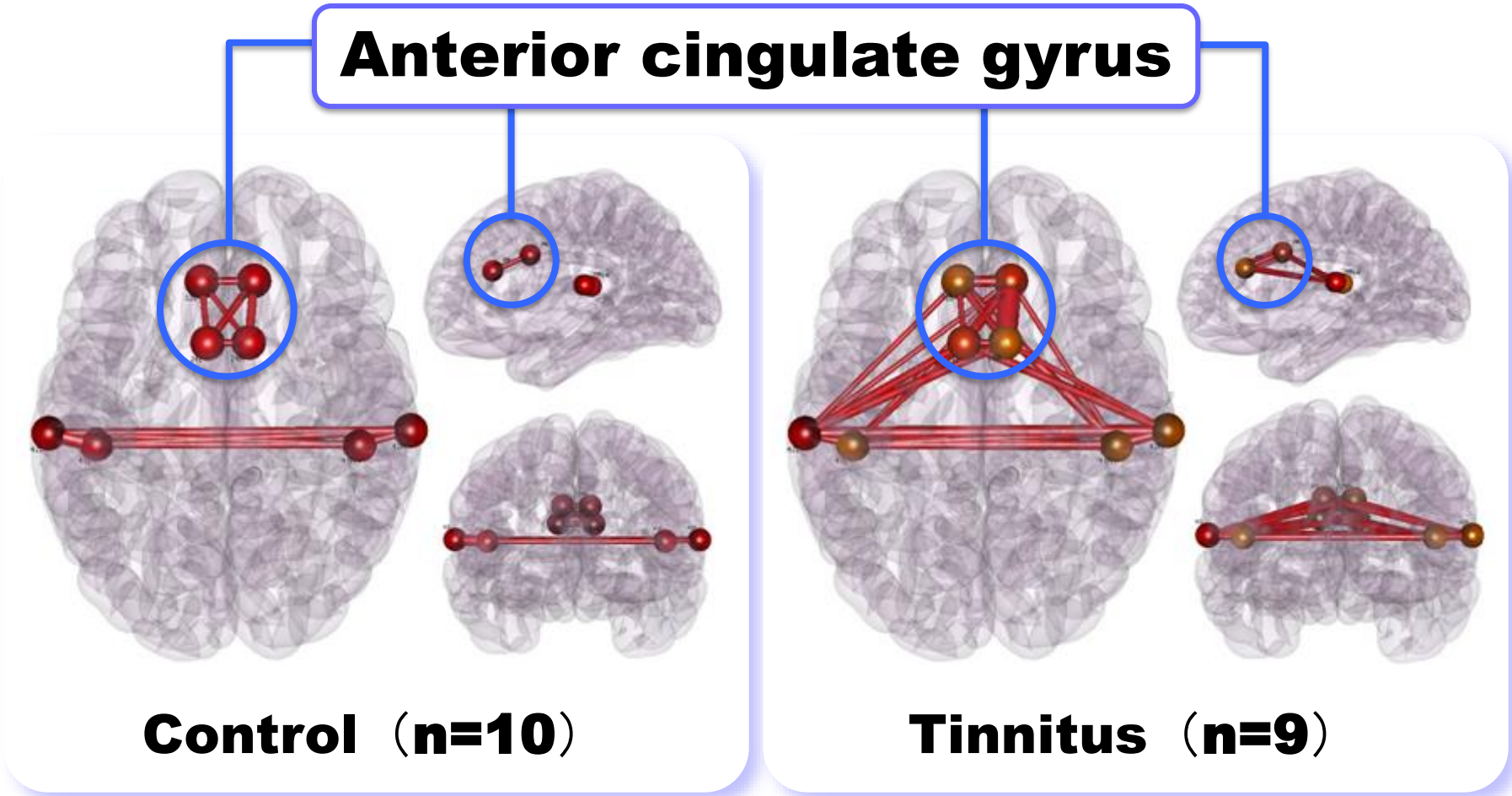
Auditory-based functional connectivity



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Tinnitus treatment

- **Treatment for tinnitus**
  - Drug therapy
  - Surgucal therapy: cochlear neurectomy
  - rTMS・tDCS
- **Treatment for tinnitus annoyance**

  Habituation therapy
  - Drug therapy: antidepressants, sleep medicines
  - Psychoterapy: cognitive-behavioral therapy
  - TRT: directive couseling + sound therapy

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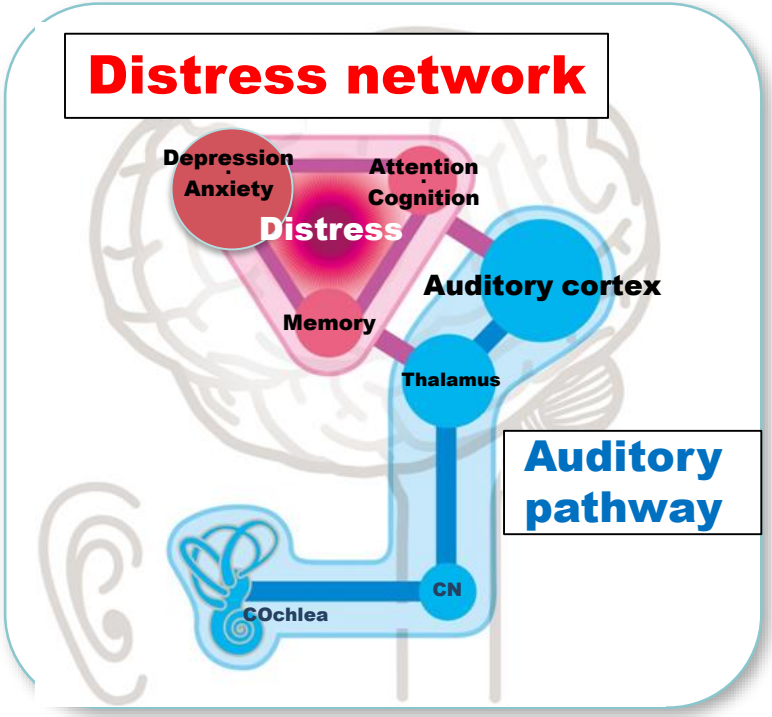
Antidepressants

- Selective serotonin reuptake inhibitor (SSRI)
- Serotonin-norepinephrine reuptake inhibitor (SNRI)
- Noradrenergic and specific serotonergic antidepressant (NaSSA)

Distress network

Improve directly "depression and anxiety" of distress network →Improve distress



Auditory pathway

Auditory pathway has an abundance of serotonin receptors.

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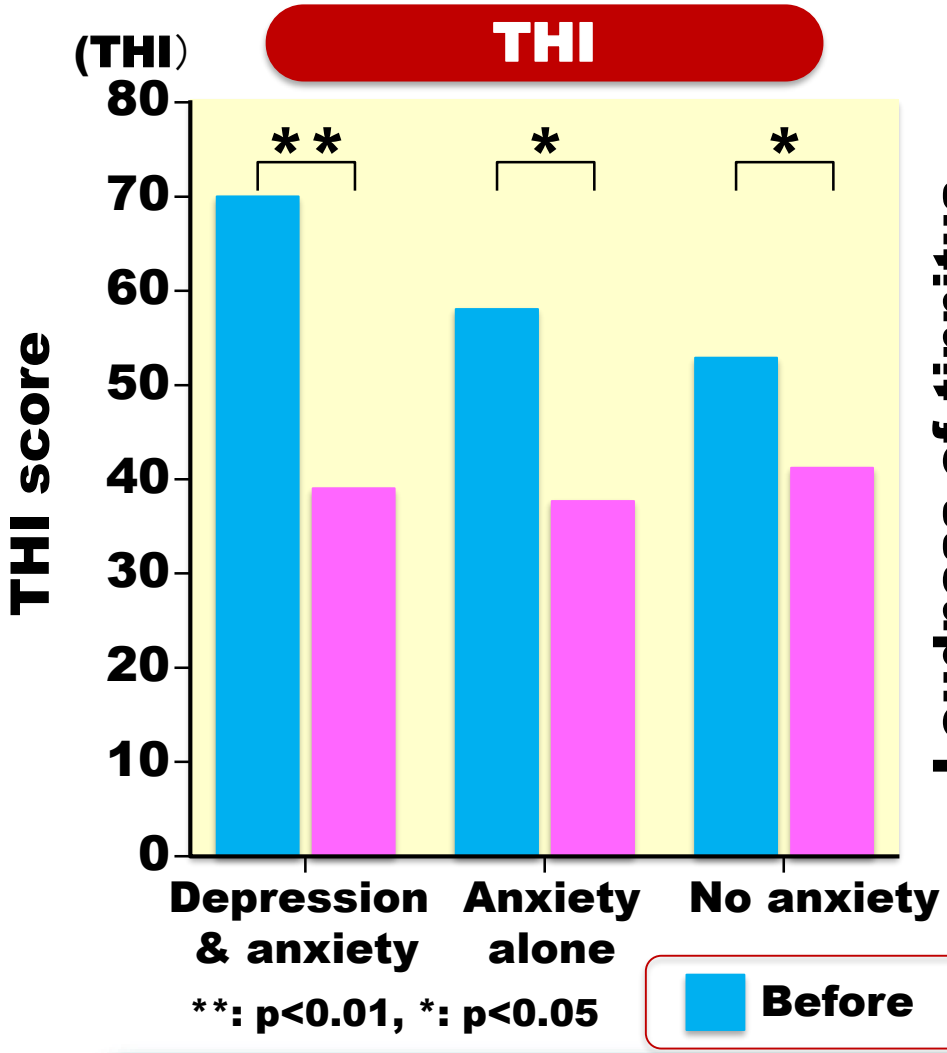
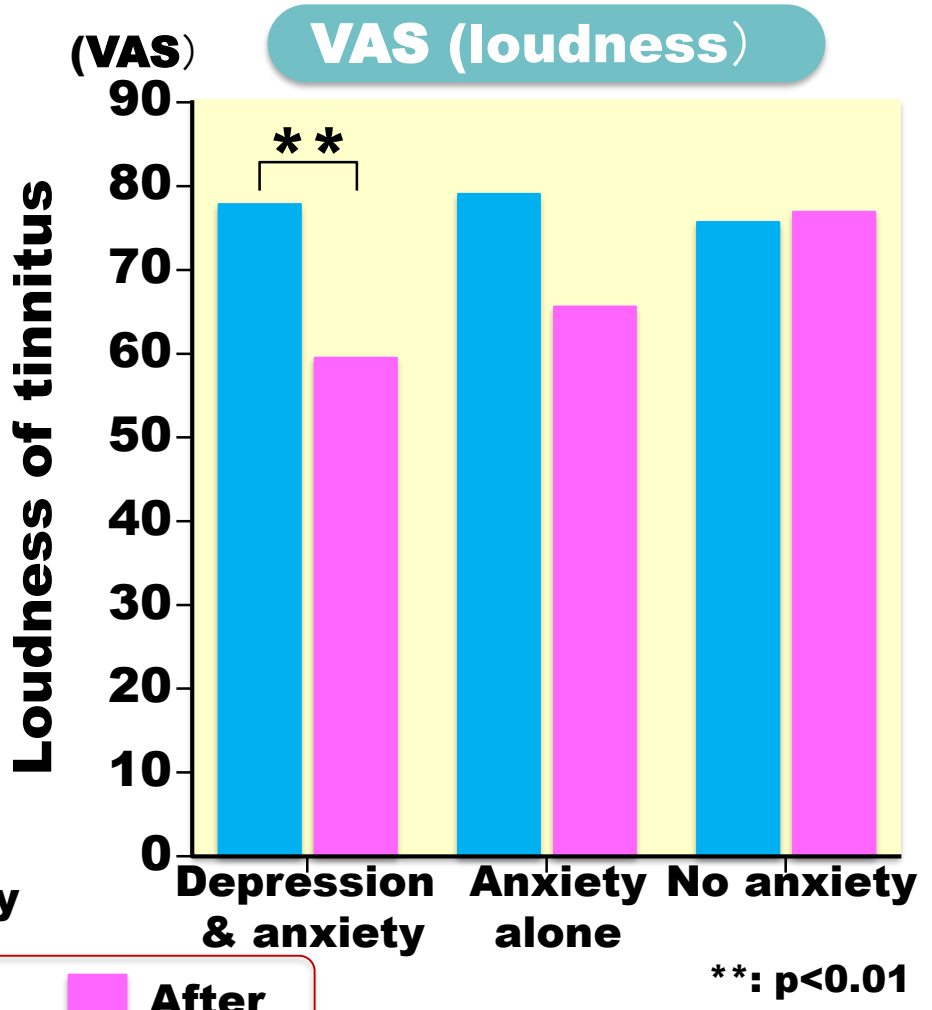
SSRI outcome

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





Before
After

Patients with depression and anxiety showed better improvement

Oishi et al. 2010

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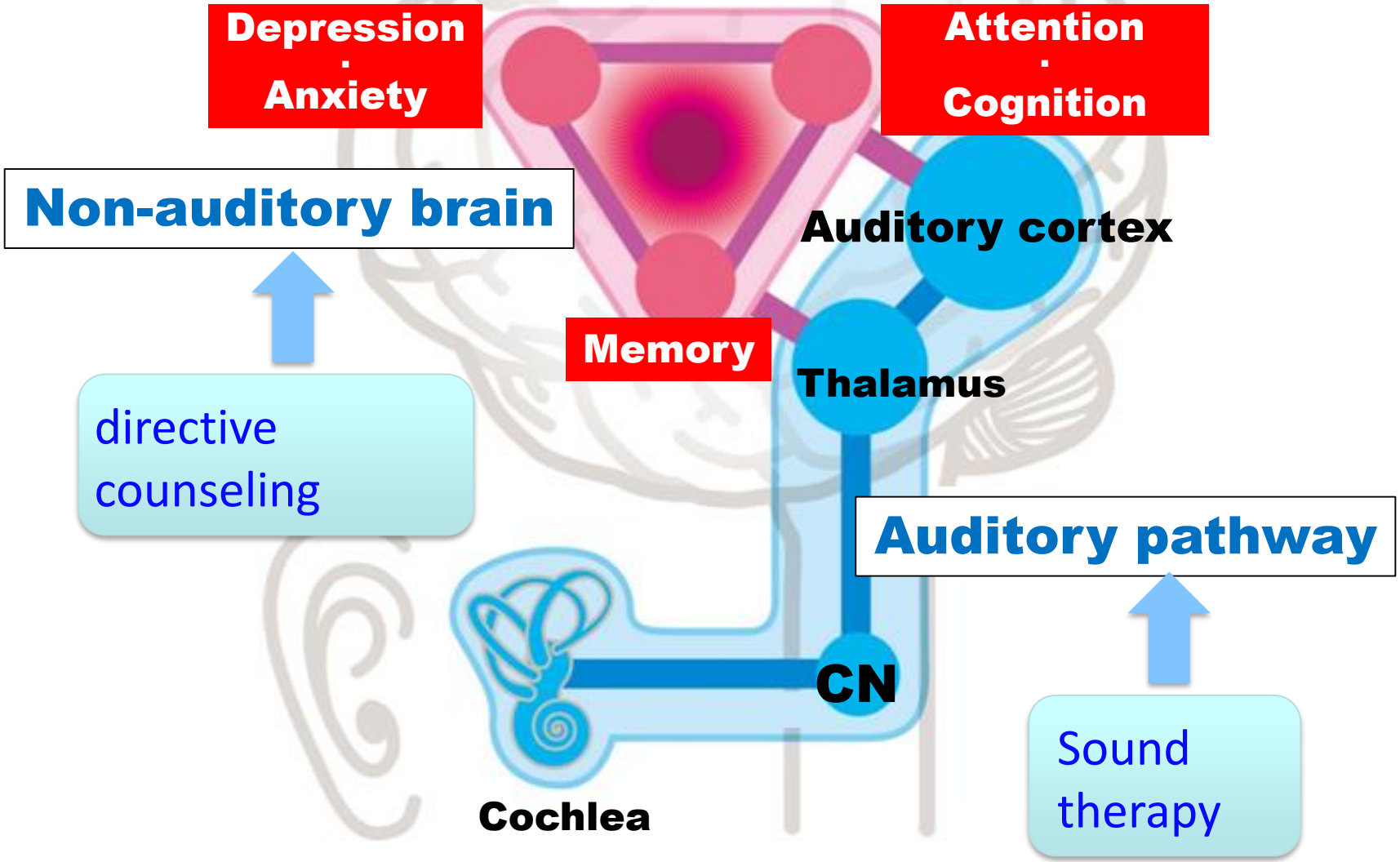
TRT



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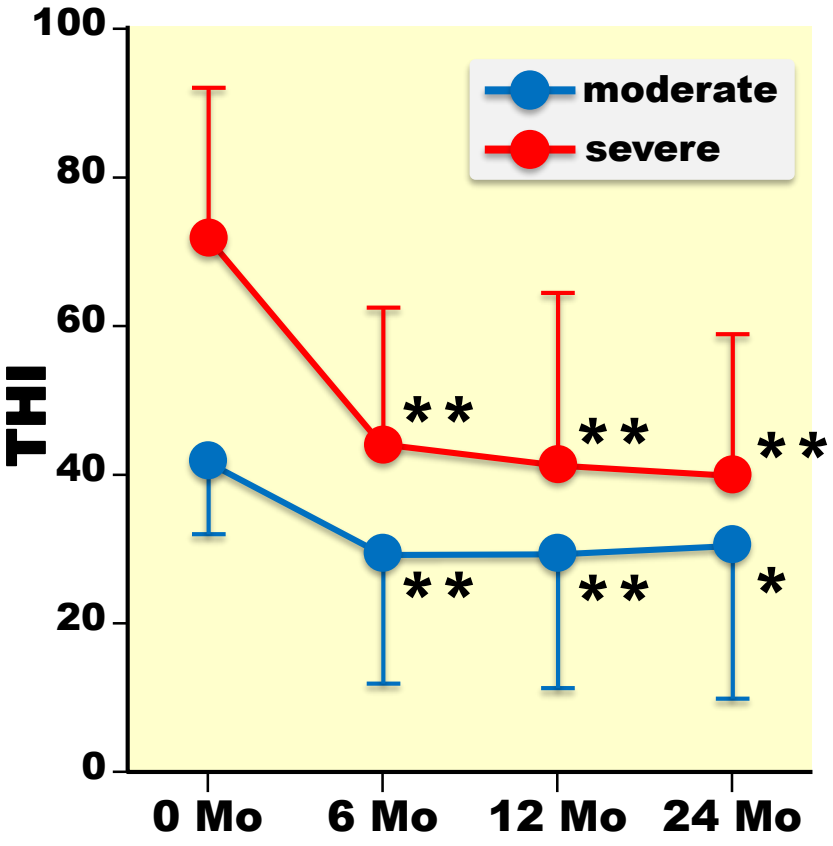
Treatment effects of SG

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



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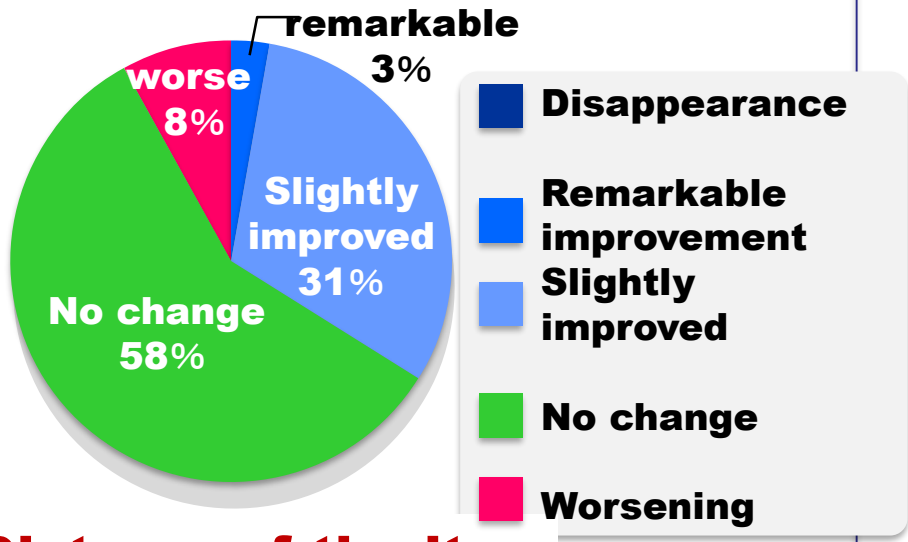
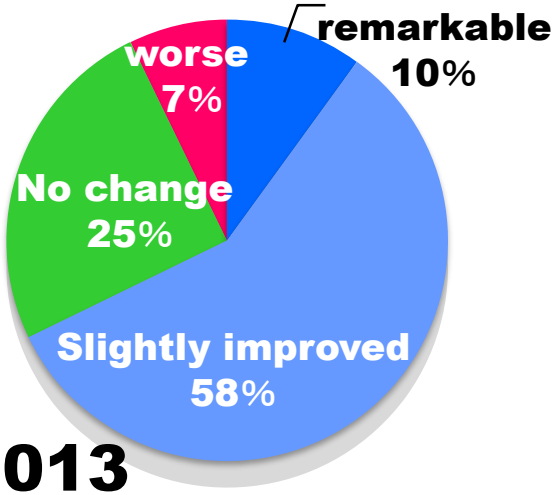
Loudness of tinnitus



Distress of tinnitus



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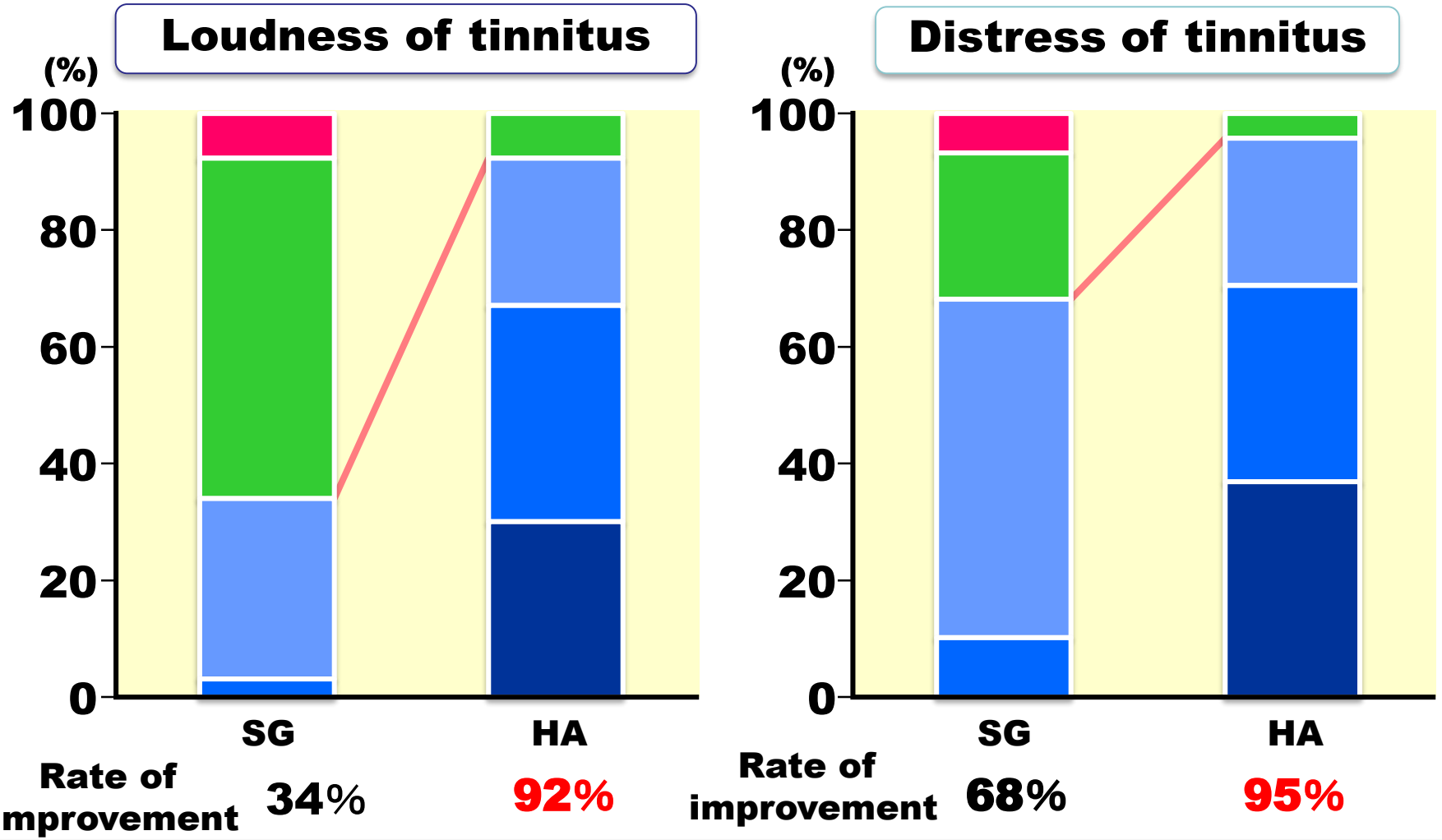
Treatment effect of HA



Rate of improvement : slightly improved≦

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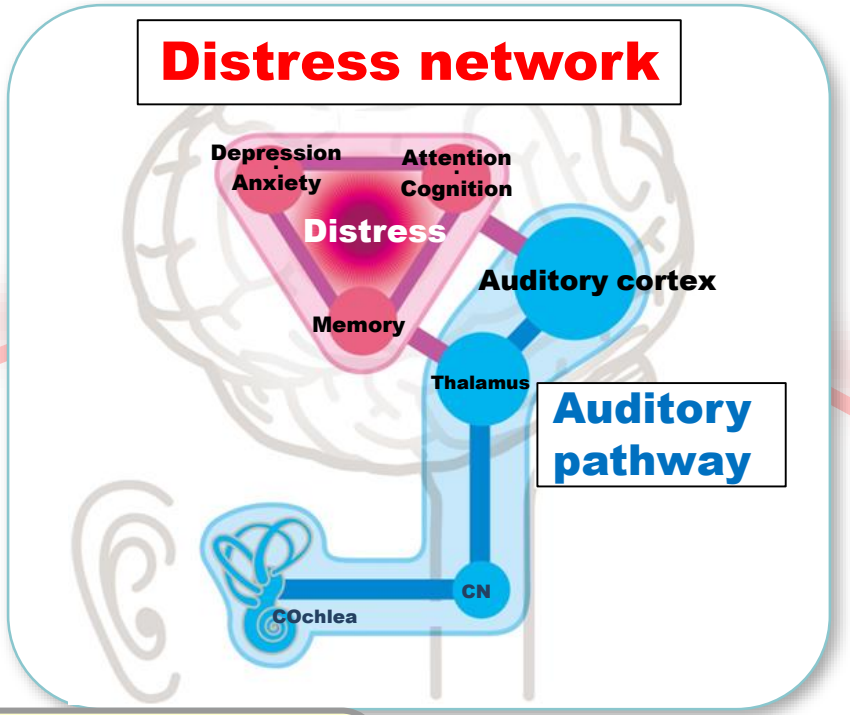
Why is sound therapy with HA effective?



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

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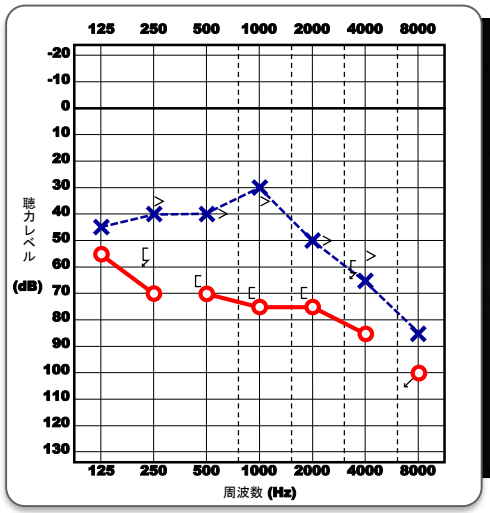
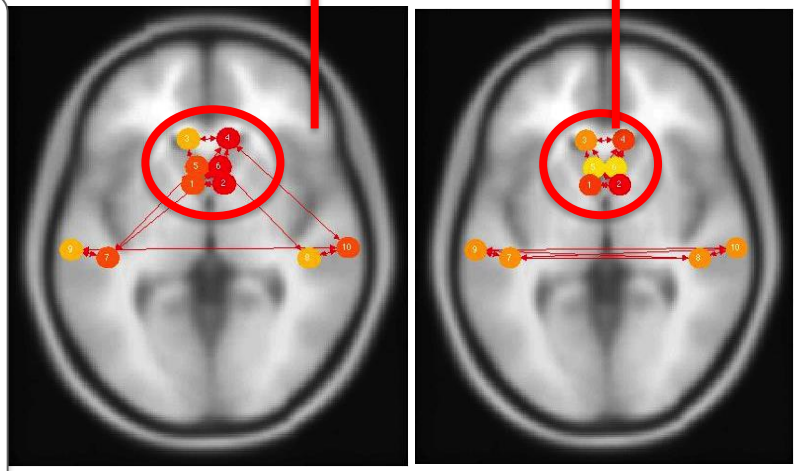
Sound therapy with HA restores the FC changes

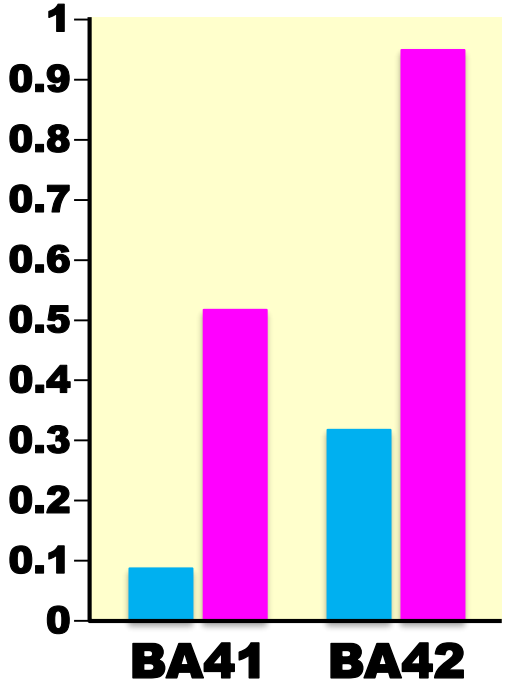
80 years old male Right tinnitus



Anterior cingulate gyrus



β-value between left and right auditory cortex



Before HA

THI 64
SDS 49
STAI
state 65
trait 54

After HA

THI 20
SDS 27
STAI
state 36
trait 41

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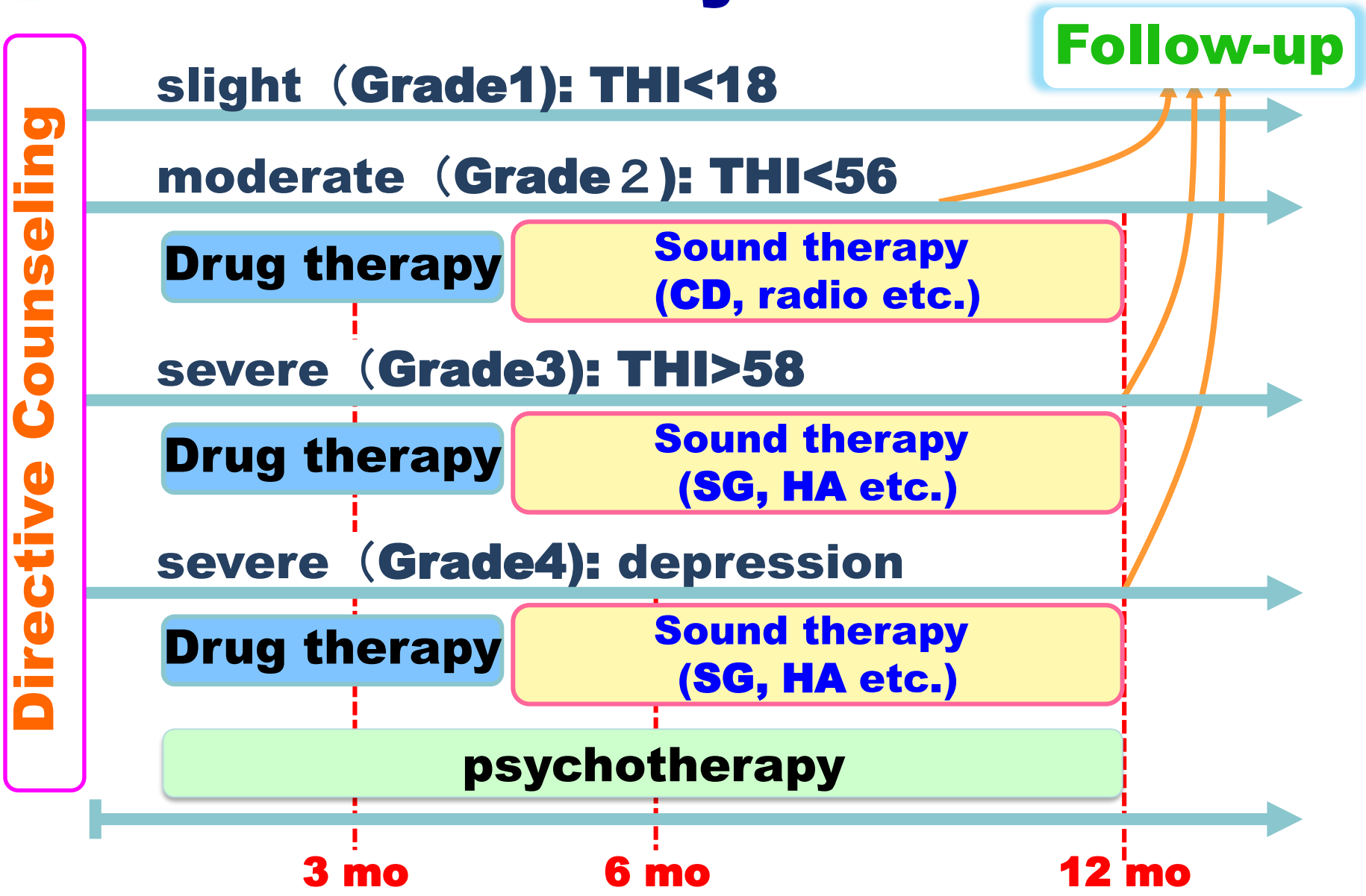
Multimodality treatment



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rTMS

Repetitive treanscranial magnetic stimulation

Basis

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

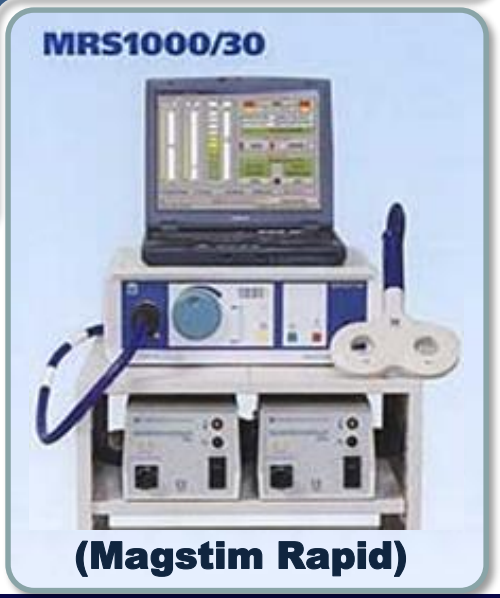
Feature

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)

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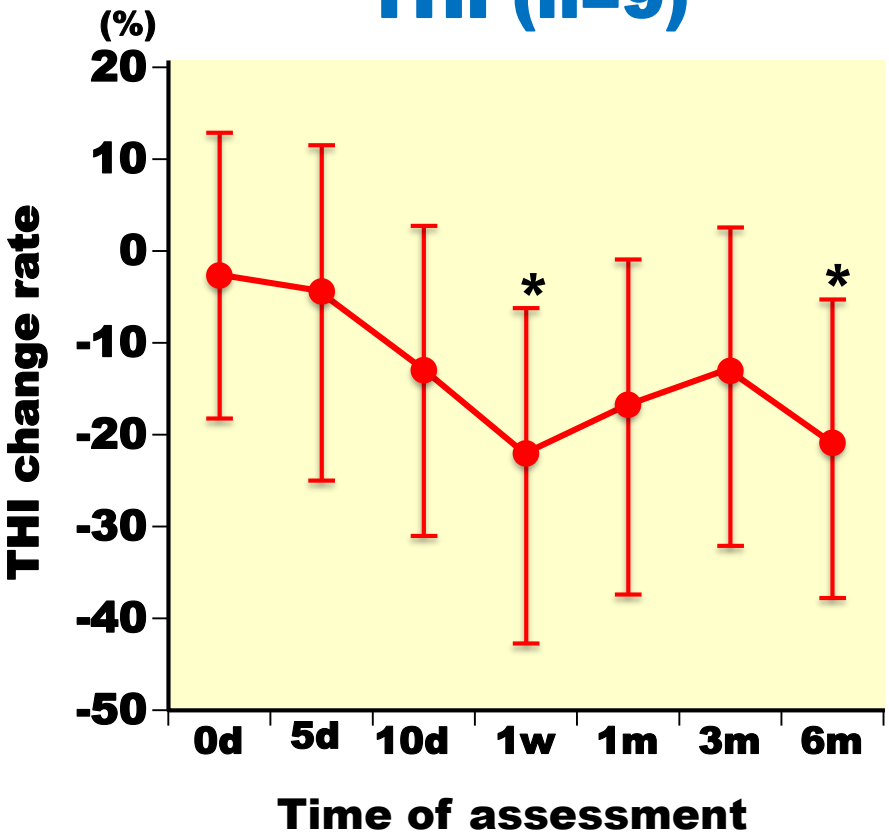
Effect of rTMS

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**

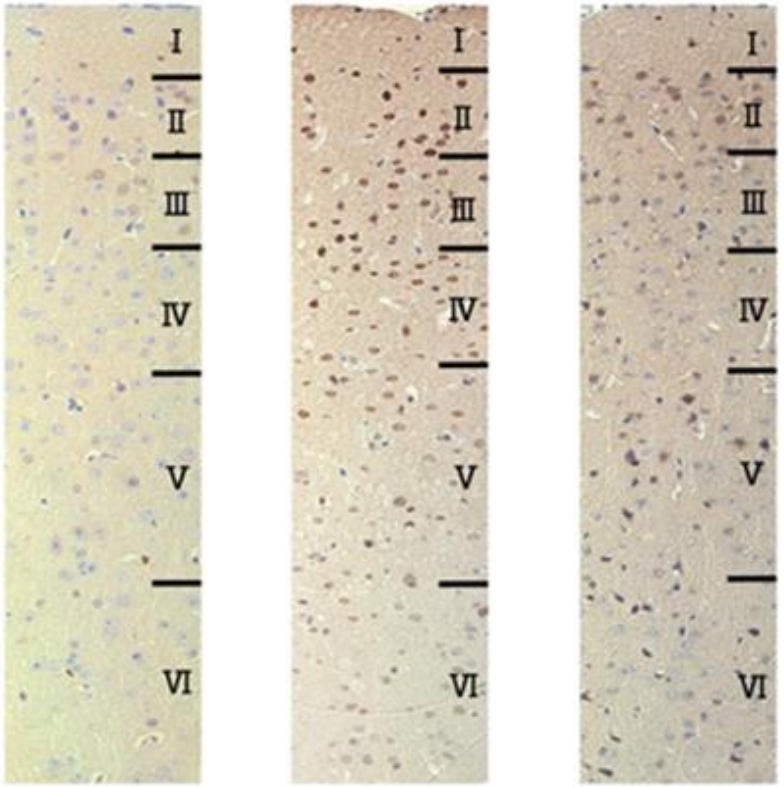
THI (n=9)



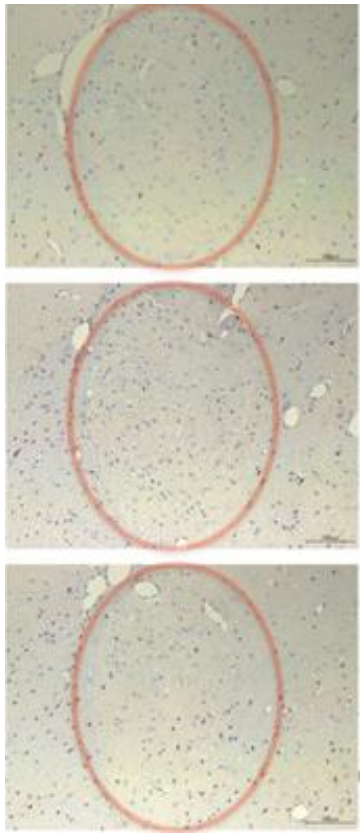
Effects of rTMS continued until 6 month later

rTMS induces c-Fos expression in auditory cortex

Left auditory cortex



Medial geniculate body



rTMS induce plasticity of auditory cortex

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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

tDCS

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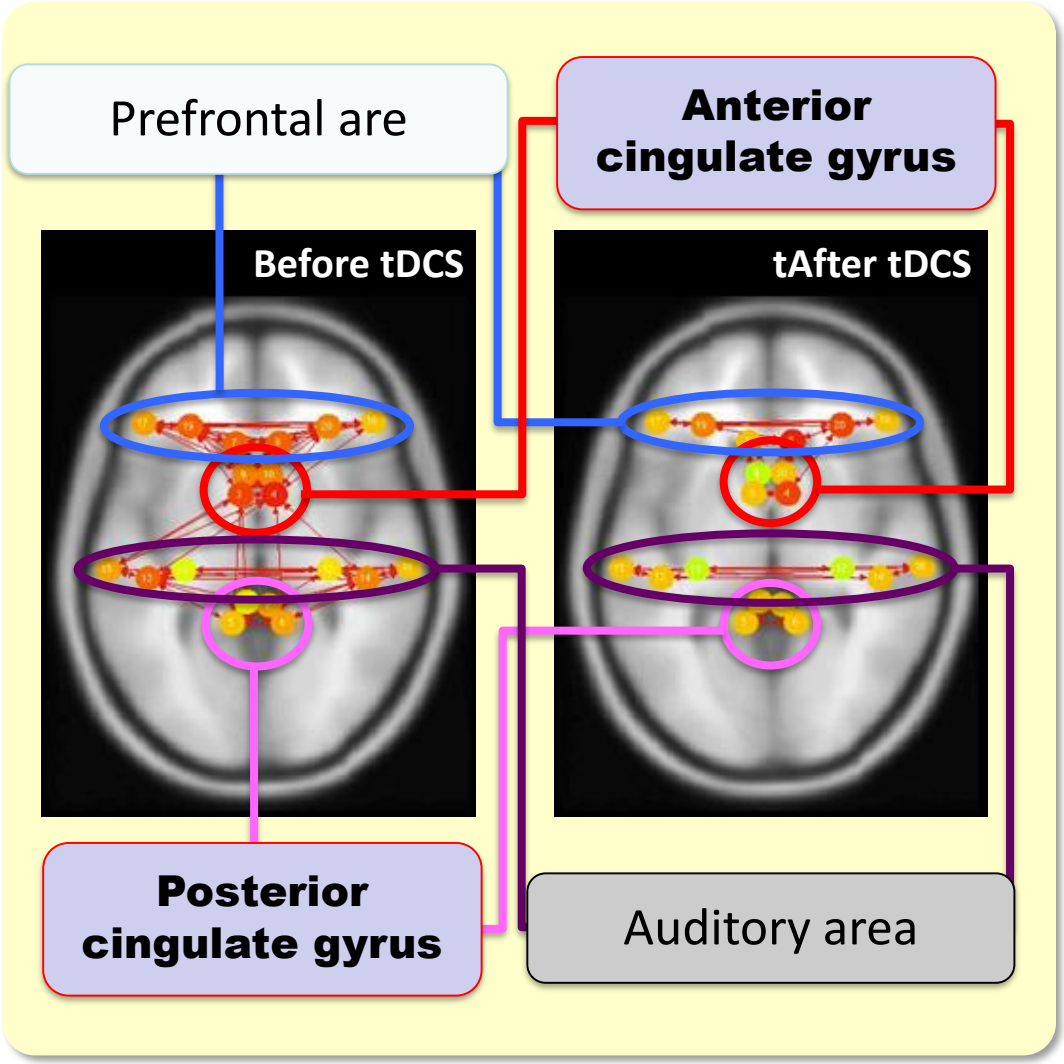
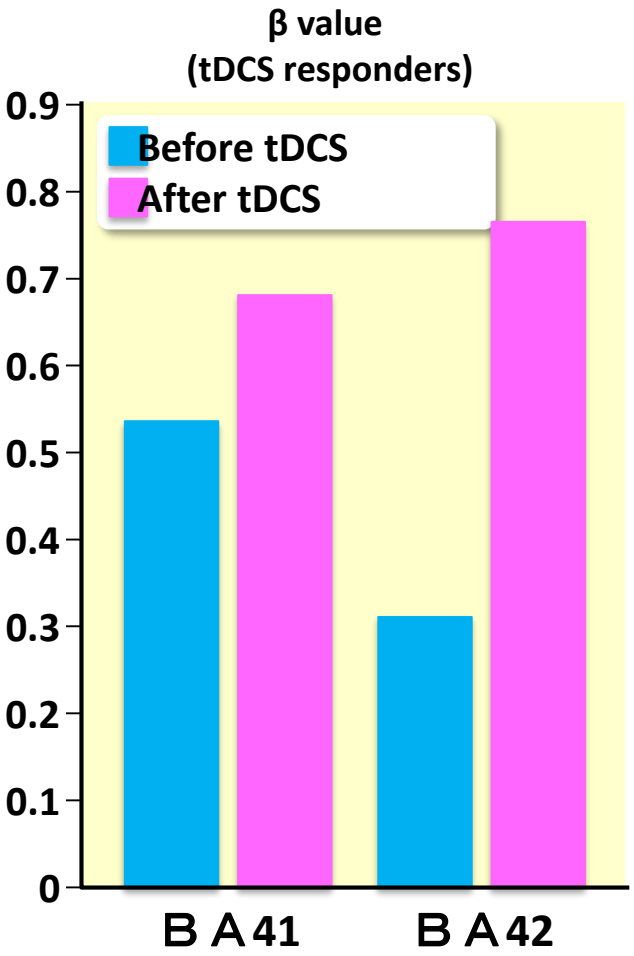
Change of fMRI after tDCS



61 y/o male



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Central management