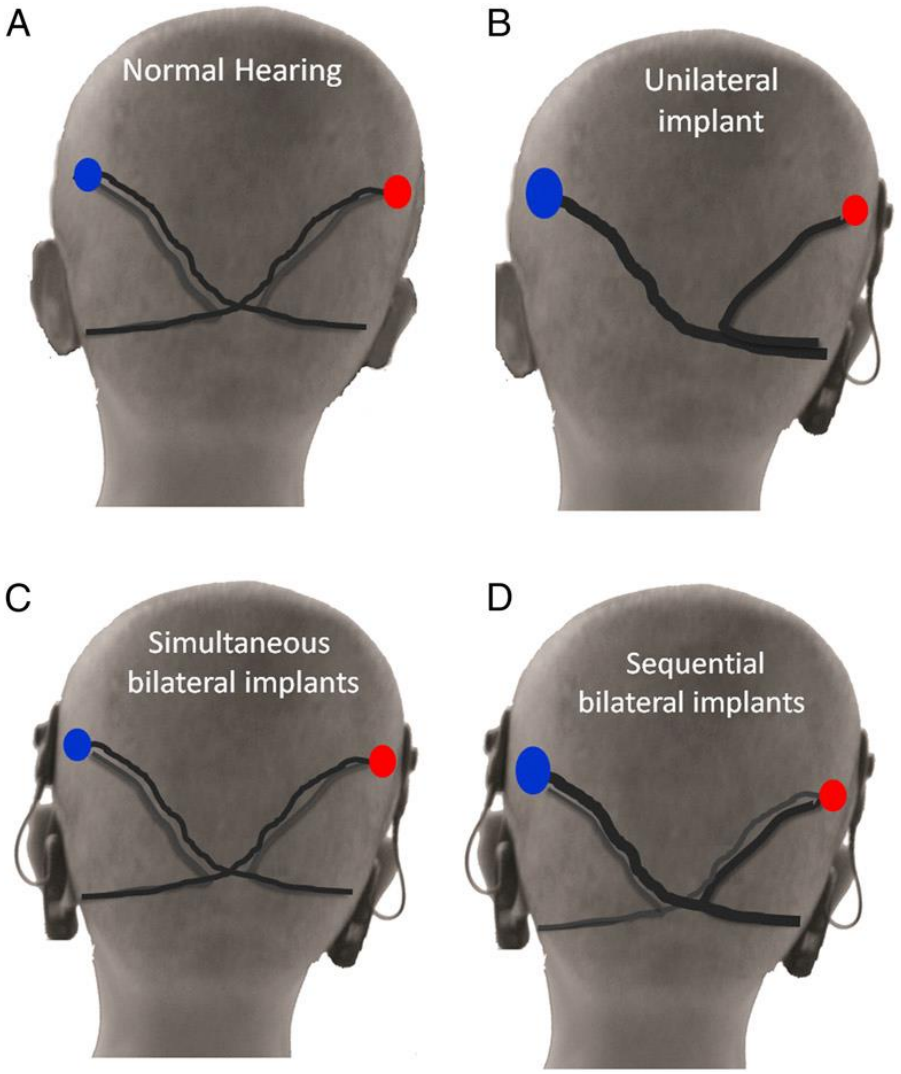
신경세포주위망 리모델링을 이용한 청각처리장애 치료
Remodeling perineuronal nets of auditory nervous system: novel therapeutic approach for auditory processing disorders

이비인후과 김소영

Contents

- Central auditory neural plasticity
  - Inter-implant intervals
- Perineuronal nets (PNNs)
- Changes of PNNs following auditory deprivation
  - Single-sided deafness
  - Noise-induced hearing loss

Central auditory neural plasticity after hearing loss



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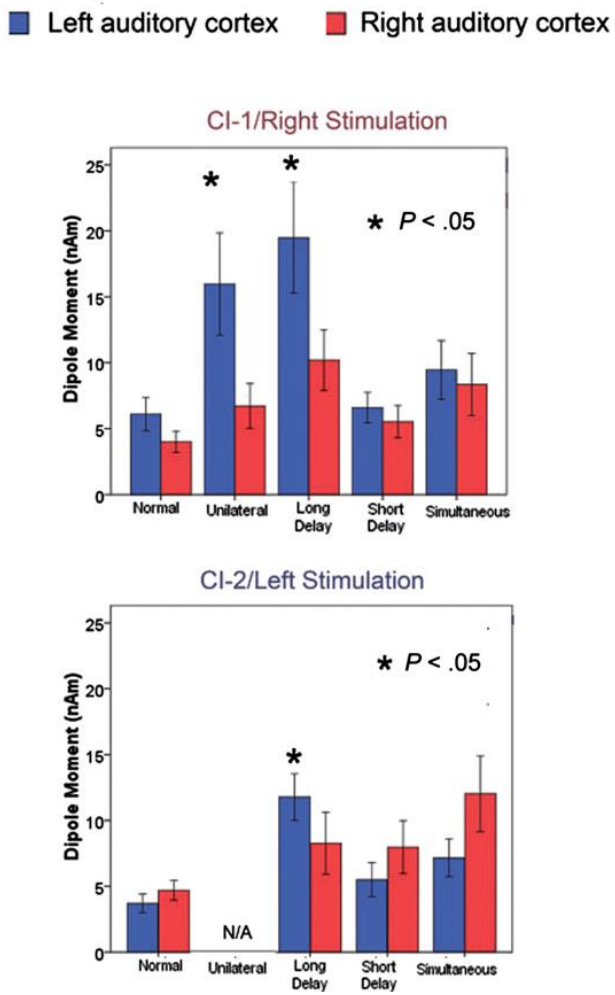
Hearing ear preference

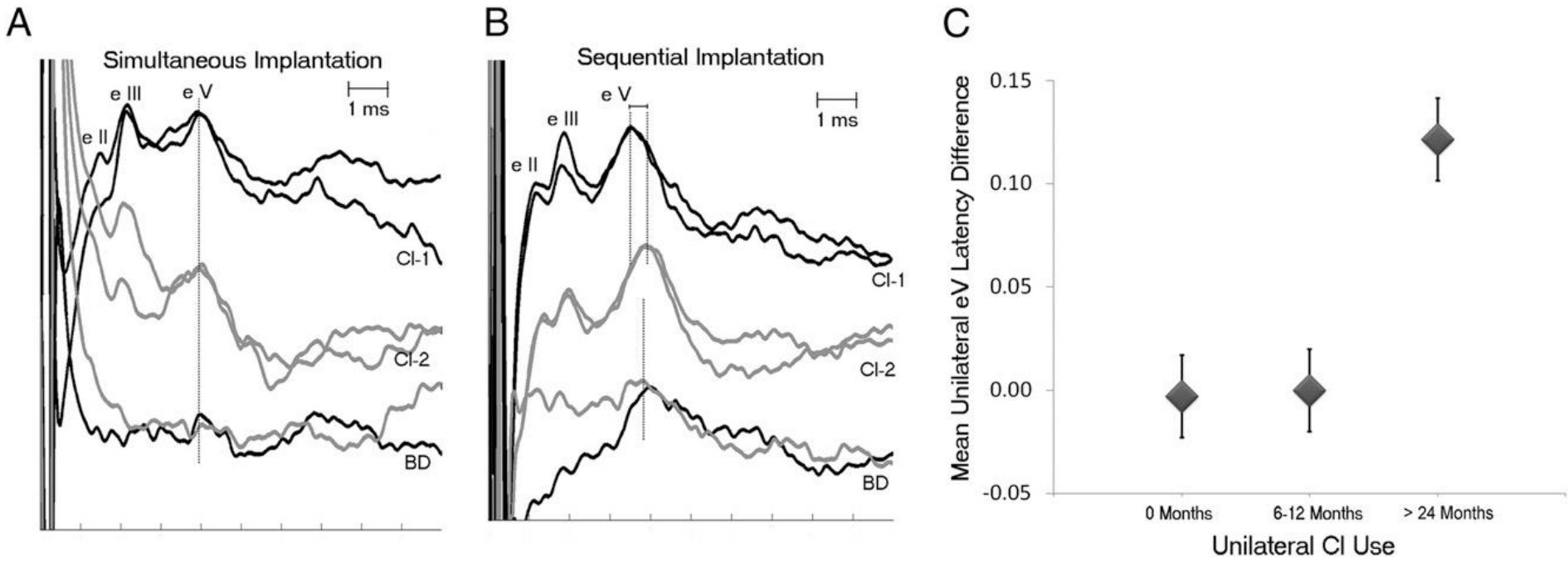


(Goron KA et al. Brain, 2013)

Central auditory neural plasticity after hearing loss

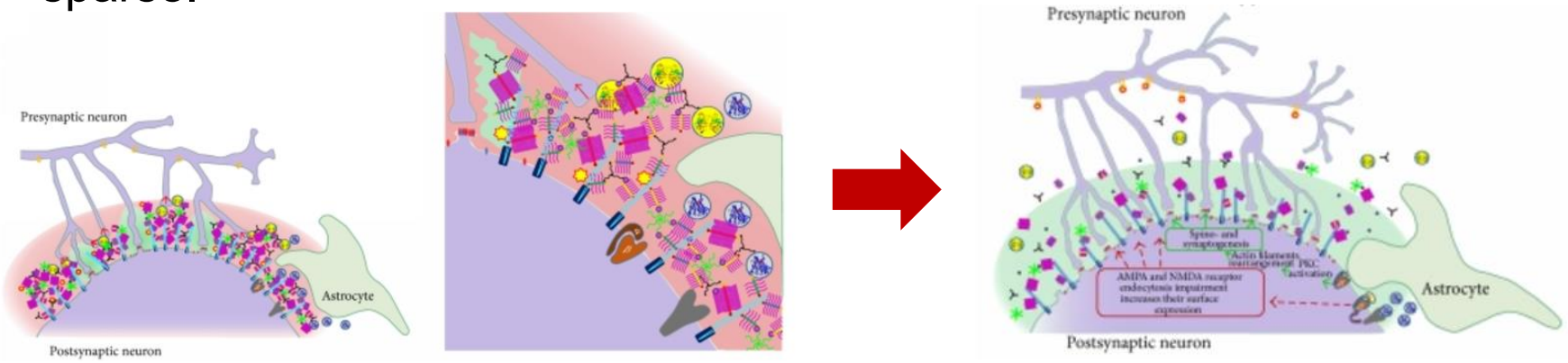
- When the opposite (second) ear was implanted after **1.5 years**, the brainstem responses from this ear remained abnormally prolonged despite up to 3 years of bilateral implant use.

(Goron KA et al. J Neurosci, 2012)



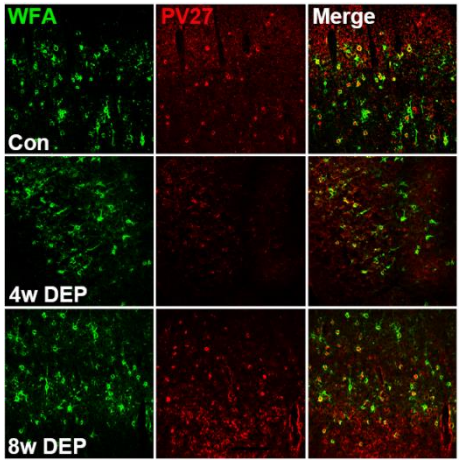
Introduction: Perineuronal nets (PNNs)

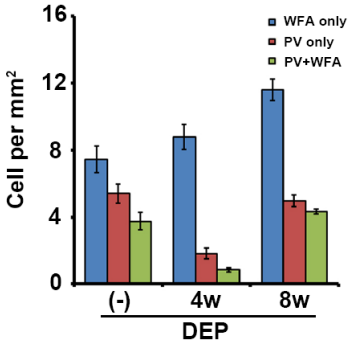
- Perineuronal nets (PNNs) are specialized extracellular matrix components that consist of chondroitin sulfate proteoglycans (CSPG).
- These CSPGs are found throughout the extracellular matrix, but are highly dense around cortical parvalbumin (PV+) GABAergic interneurons.
- While PV/PNN expression has been well studied in somatosensory and visual cortex of rodents, focus on A1 is relatively recent and sparse.

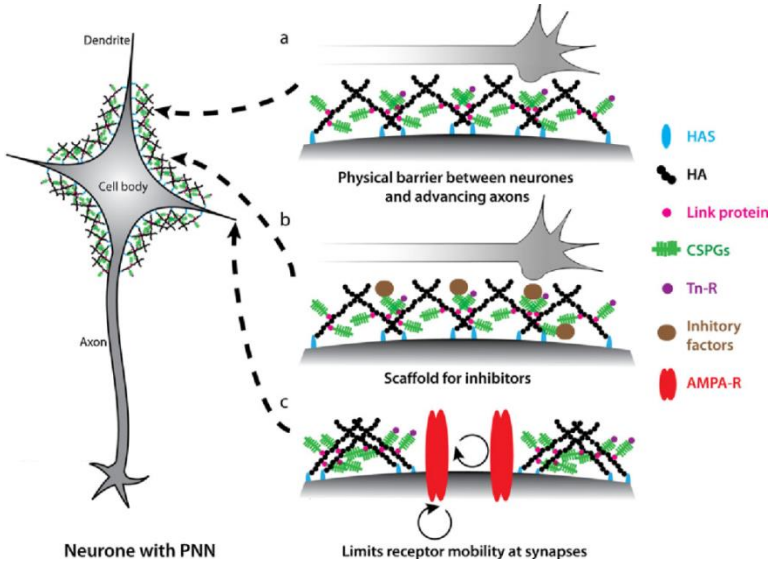


Introduction: Roles of PNNs

- PNNs protect PV+ inhibitory neurons from oxidative stress.
  - Diesel extracted particle (DEP) activated oxidative stress and inflammation and induced decreased number of interneuron and unwrapped with PNNs. *(Kim et al., Neurotoxicology, 2018)*
- PNNs stabilize synapses and limit neuroplasticity. The PNNs are fully developed and reach adult patterns at approximately 3 - 5 weeks of age, representing the end of the critical period that permits neural plastic changes. *(McRae,P.A. et al., J.Neurosci, 2007)*

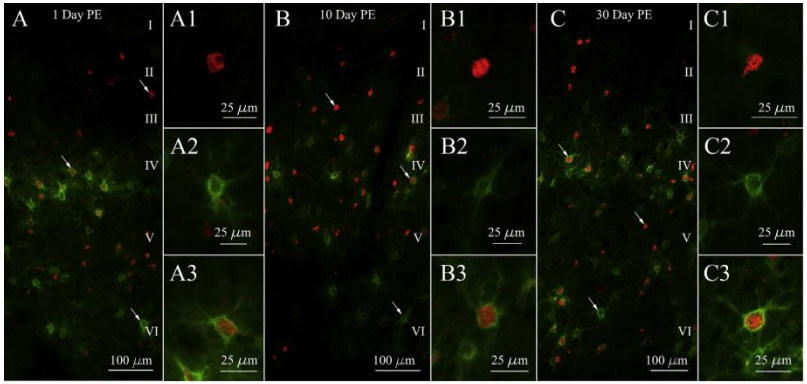


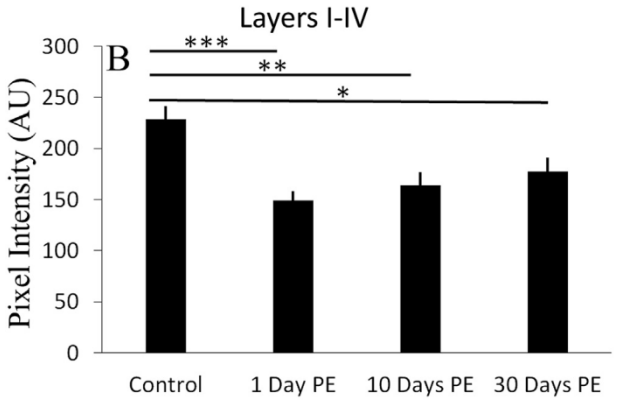




Introduction: PNNs in the auditory system

- Recent studies reported that a significant increase or decrease in PNN intensity of deaf side following hearing loss. *(Congli Liu et al. 2018)*
- Neonatal conductive hearing loss has been shown to disrupt the development of Cat-315-reactive PNNs in the rat superior olivary complex. *(Myers et al., Brain Res, 2012)*
- Although the PV-positive cell densities were not changed, the PNNs density attenuation was lasted at least 30 days following noise exposure. *(Anna Nguyen et al., Hear Res, 2017)*





Introduction: Cortical disinhibition after hearing loss

- Hearing loss is associated with increased excitability in the central auditory system, but the cellular correlates of such changes remain to be characterized.
  - Molecular studies indicate that in the brainstem, after 2 – 5 days post trauma, the GABAergic activity is largely unchanged.
  - At 2 months post trauma, excitatory activity remains decreased but the inhibitory one is significantly increased.

(Jos J. Eggermont, 2016)

	0 h	2-5 d	16 d	32 d	59 d	145 d
VCN ipsi		⇓	⇑	↑	⇓	↑⇑
DCN ipsi	⇓↓≈	⇓↓⇑	⇑	⇑↑⇑	⇓⇑↓	⇓↑⇑
IC ipsi		↓	↓⇑			
IC contra	↓≈	↓	↓⇑	⇓	⇑⇑	⇑⇑↓
A1 ipsi	⇓↓	↓⇑	↓⇑	↓⇑	⇑	
A1 contra	⇓≈↑	⇑↑	⇑↑	↓⇑↑	⇑↑	

⇓⇑ excitation (down, up); ↓↑ inhibition (down, up); ⇓⇑≈ SFR (down, up, no change); ↑ρ (up)

- The increase of excitability in the primary auditory cortex (A1) following noise exposure has been suggested to be caused by the disinhibition.

(Llano,D.A. et al., J.Neurosci, 2012)

Objectives

Hypothesis

1. Unilateral hearing loss may induce reactive changes of contralateral synaptic changes accompanied with remodeling of PNNs.
2. Increased cortical excitability in noise-induced hearing loss could be related with the attenuation of PNNs.
3. Hearing impairment after as well as before the critical period might be also accompanied by neural plastic changes.

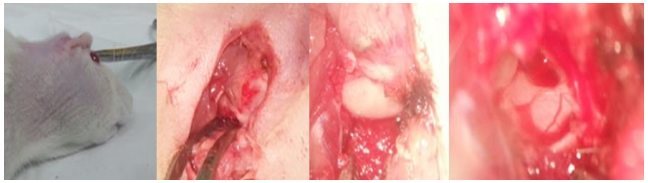
Experiments in hearing loss models,

1. To investigate the excitatory and inhibitory changes
2. To explore the changes of PNNs
3. To evaluate the degradative enzymes of PNNs

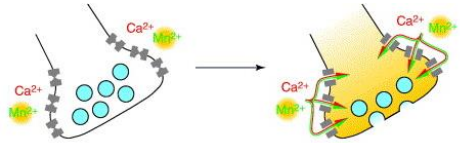
Single-sided deaf: neural activity changes

Neural plastic change of cortical and subcortical auditory neural pathway

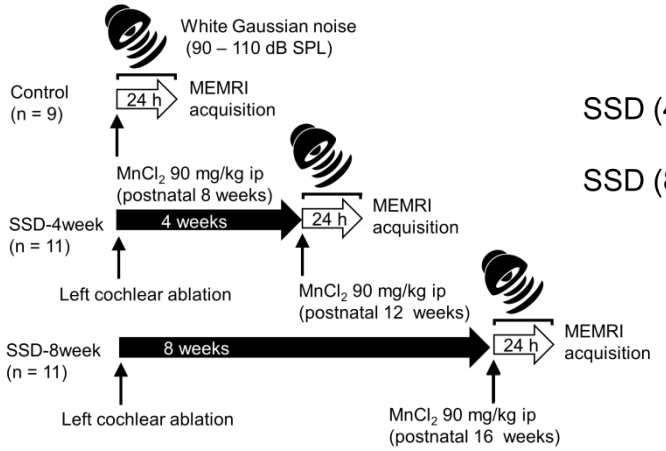
Male B57BL/6 mice (postnatal 8 weeks old)

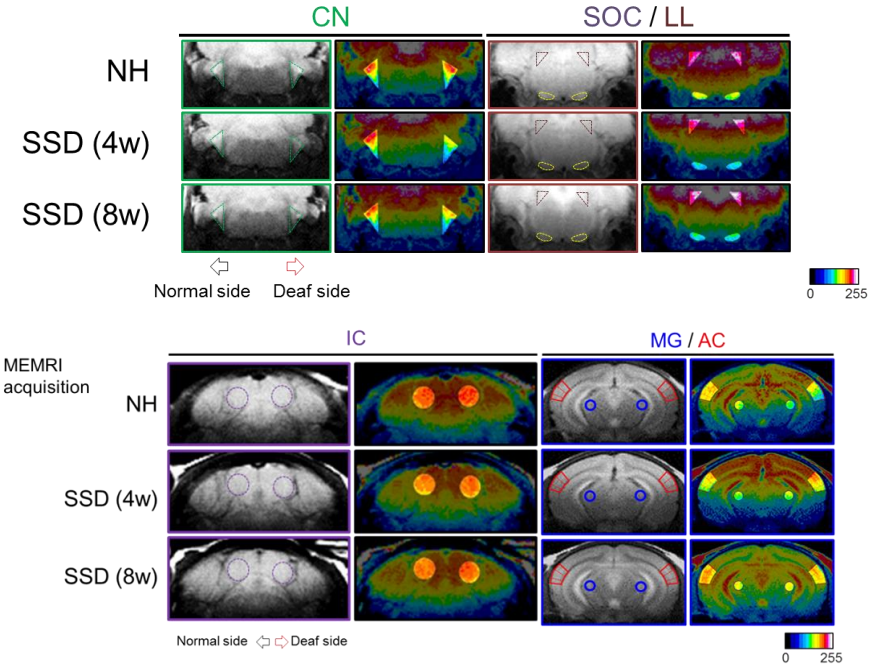


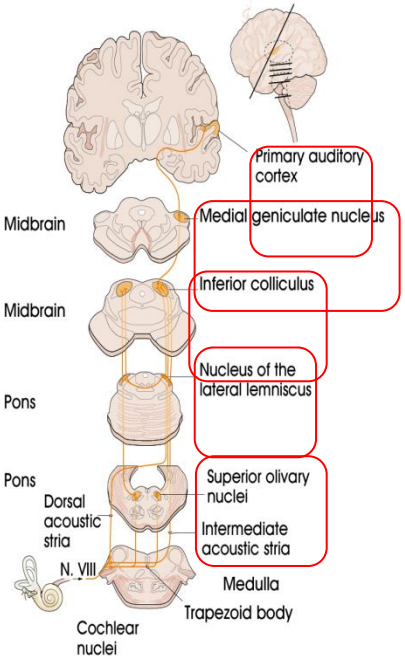
Mn-enhanced magnetic resonance imaging (MEMRI)



cochlear ablation surgery

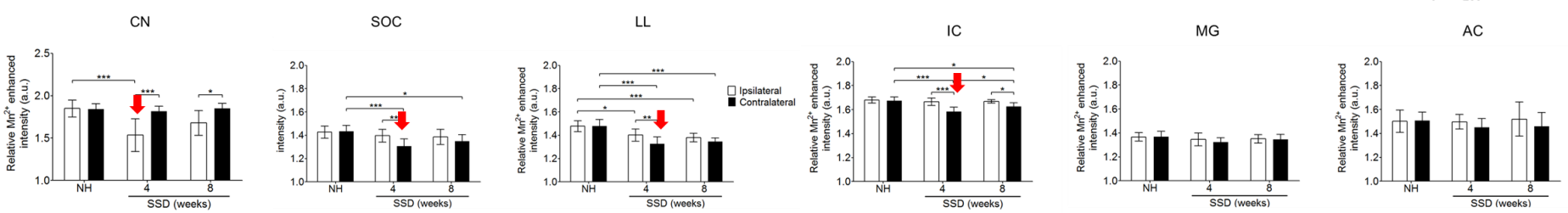




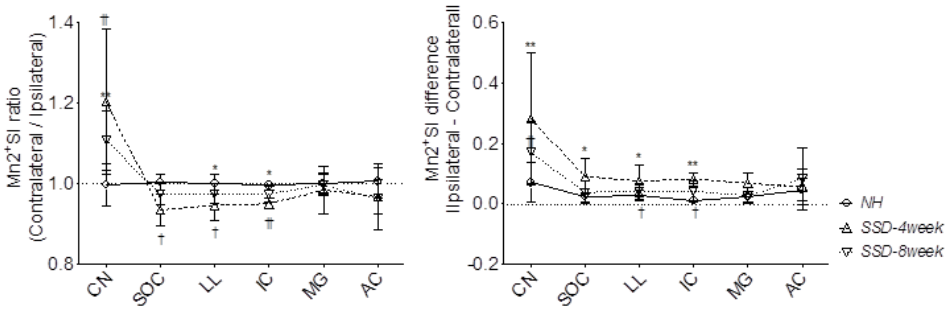


Single-sided deaf: neural activity changes

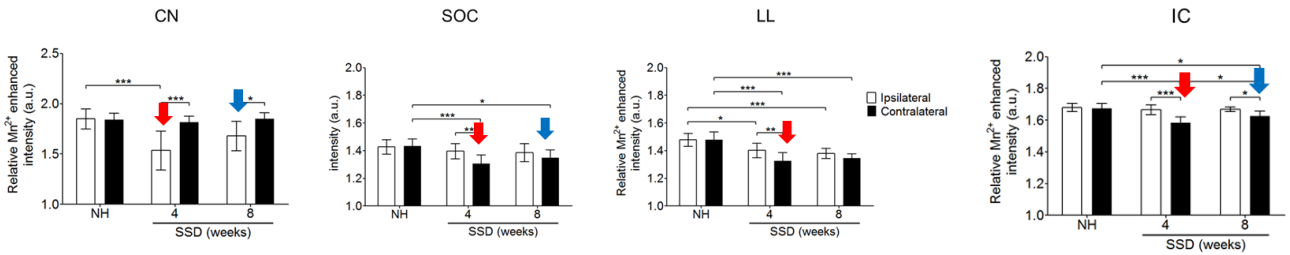
1. Aural dominance changes following SSD



2. Dilution of aural dominance in higher levels of the auditory neural system



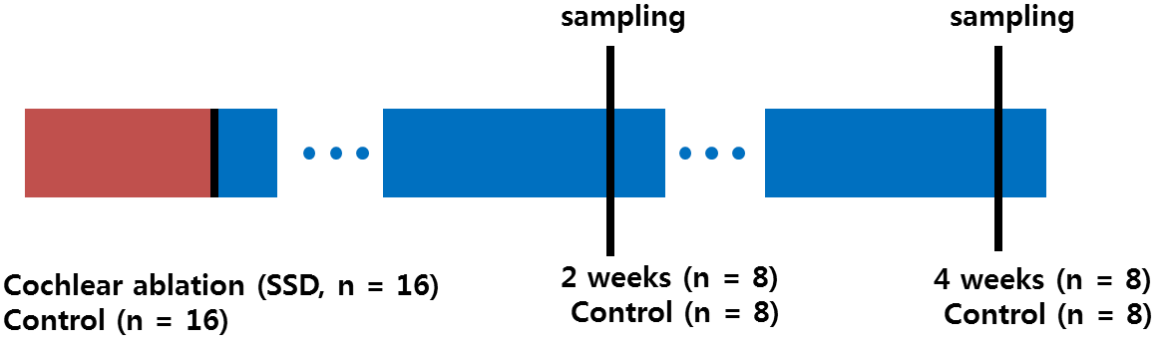
3. Attenuation of neural plastic changes with duration of SSD

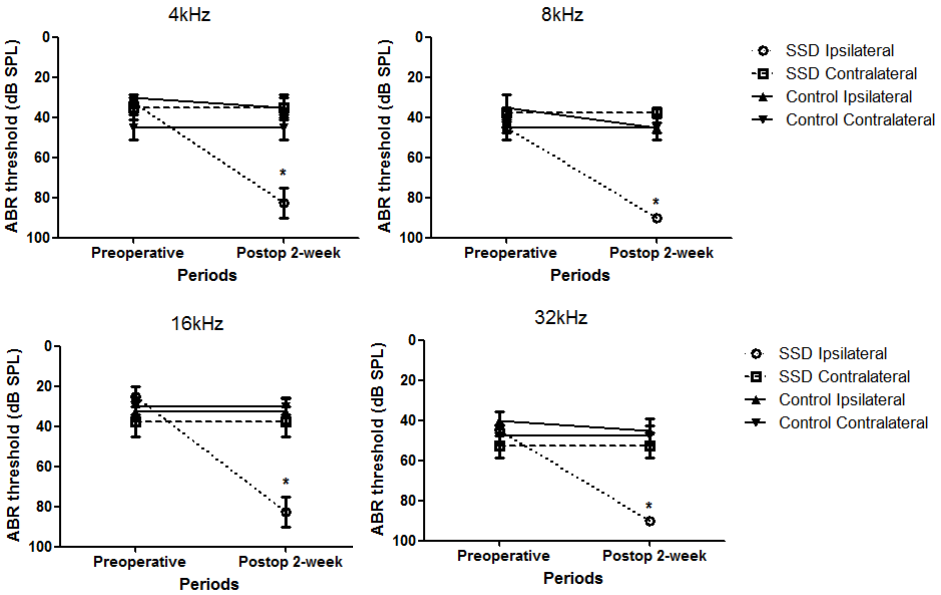


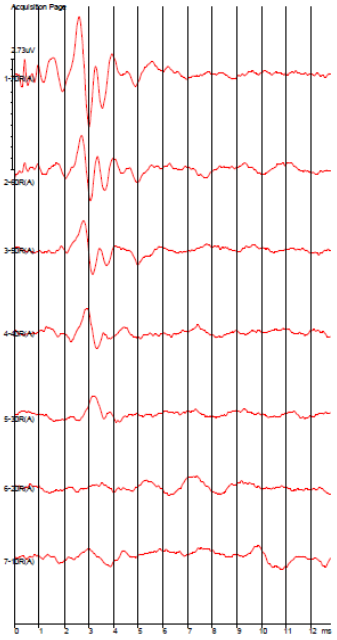
(Kim et al., Biomed Res int, 2018)

Single-sided deaf: Animal exposure

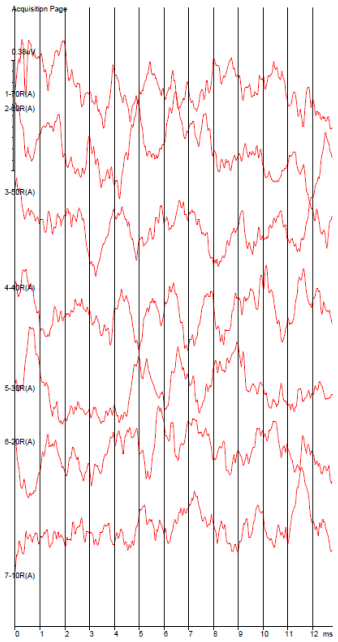
- 8 weeks Female SD rats



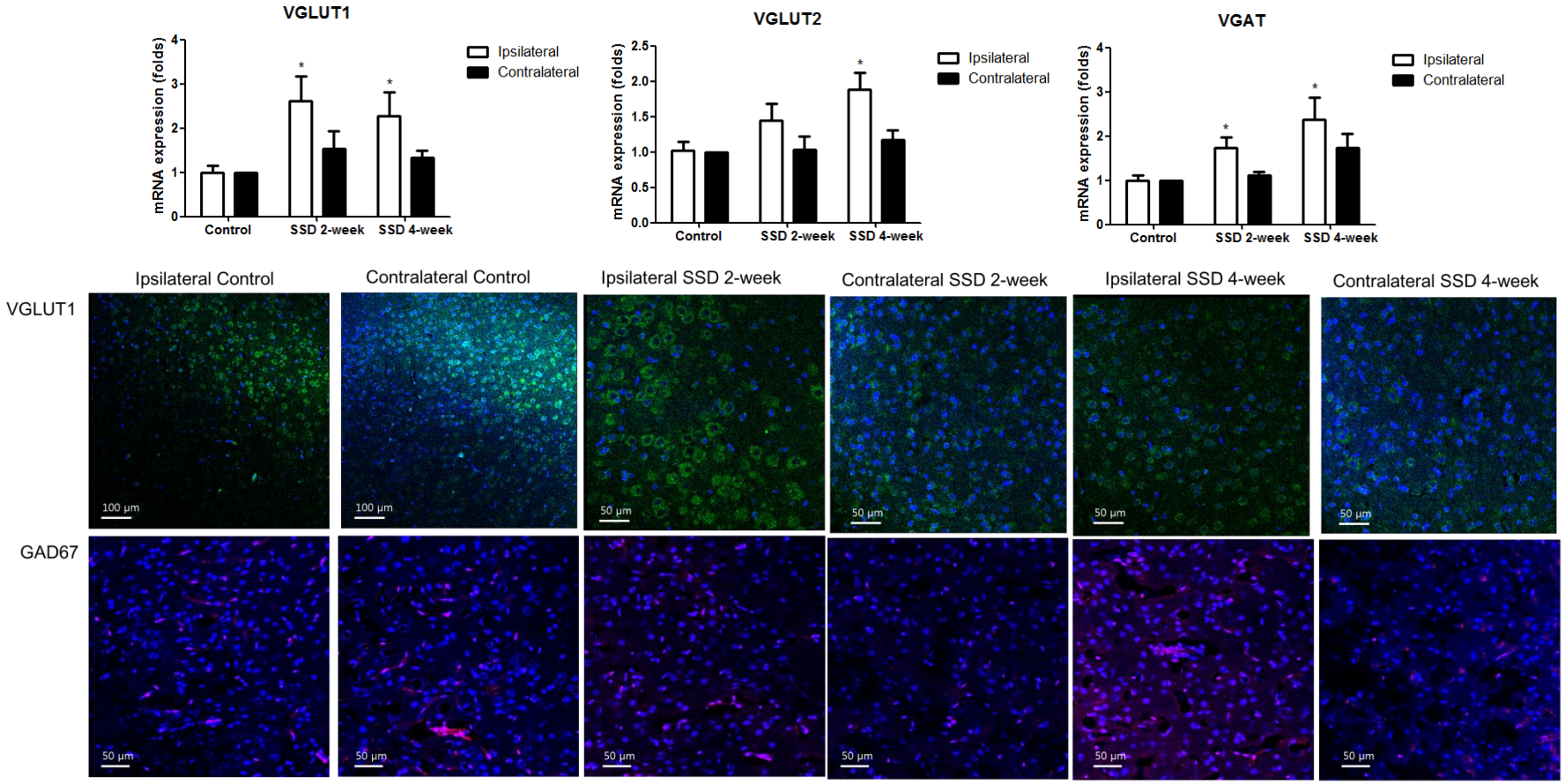




Cochlear ablation

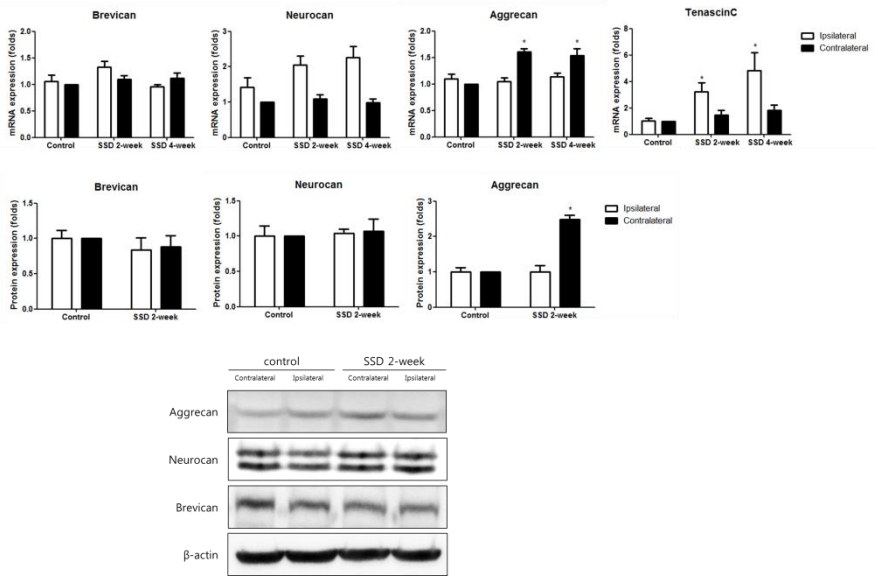


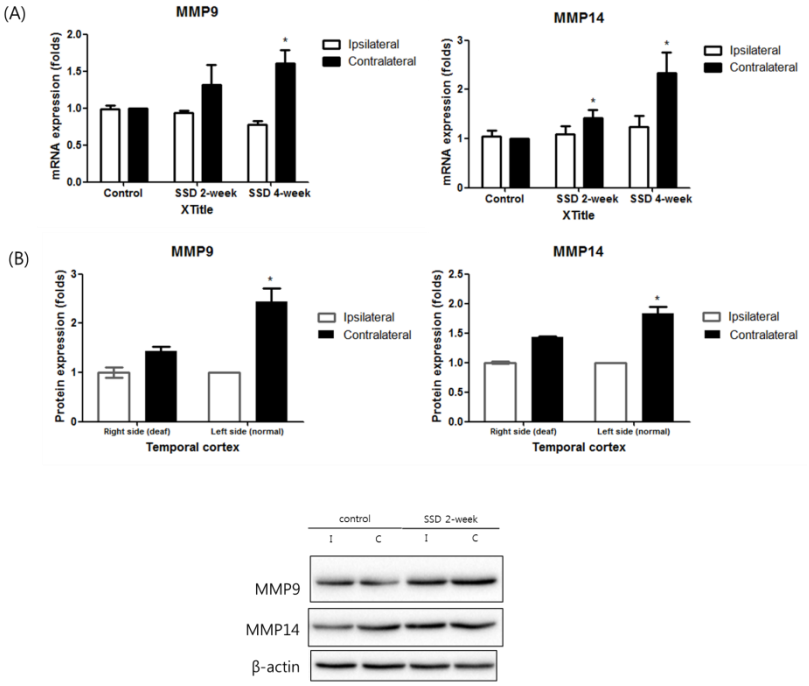
Single-sided deaf: vesicular neural transporters



- Both excitatory and inhibitory vesicular transporter expression levels were increased after SSD in the ipsilateral side of A1.
- Auditory deafferentation in the contralateral side and the compensatory potentiation of the ipsilateral cortical auditory nervous system.

Single-sided deaf: PNNs

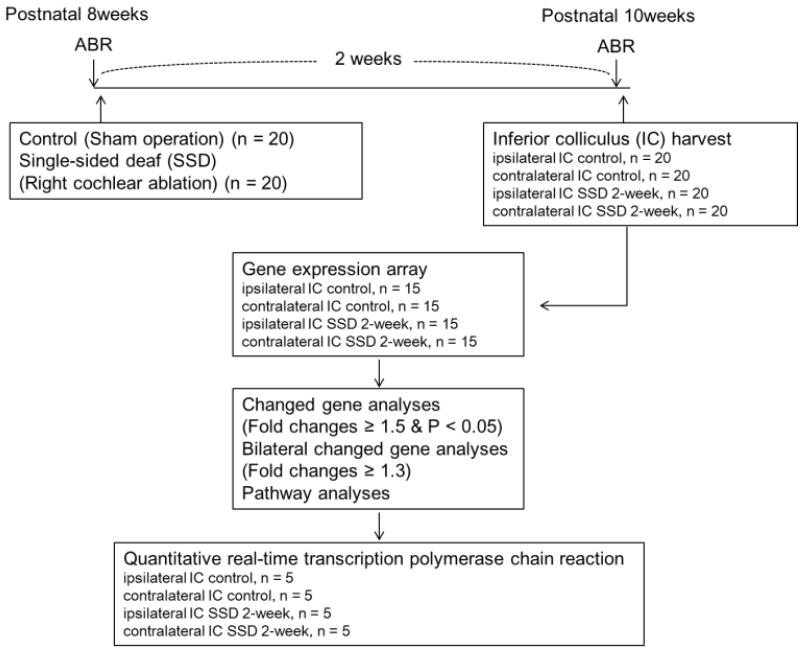




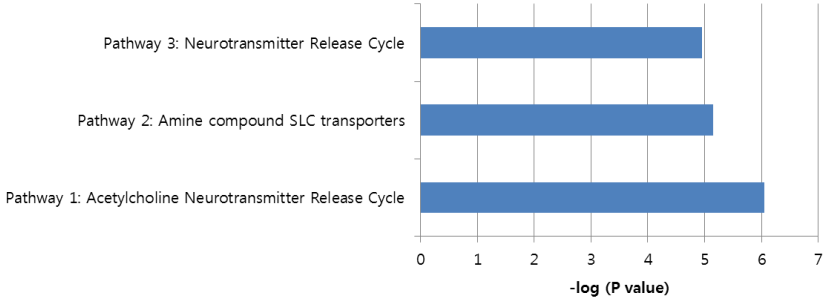
- The components or related molecules of PNNs, including aggrecan, MMP9, and MMP14 were increased after SSD in the contralateral side. The mRNA expression levels of neurocan and tenascin-C were increased after SSD in the ipsilateral side.
- The auditory deprivation induced the degradative changes of PNN in the contralateral side (dominant side after decussation) and the synthetic changes of PNN in the ipsilateral side (non-dominant side after decussation) of A1.

(Kim et al., submitted)

Single-sided deaf: Subcortical changes

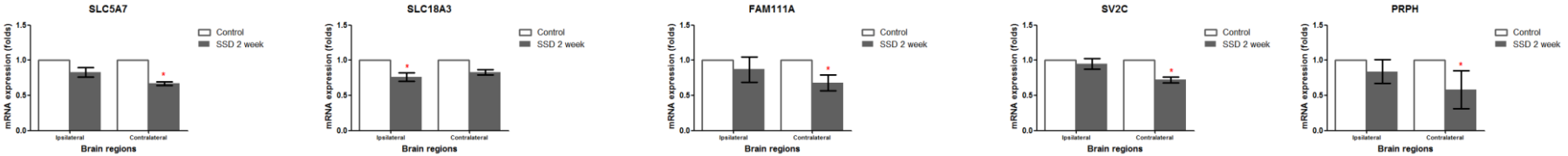


Bilateral down-regulated pathways



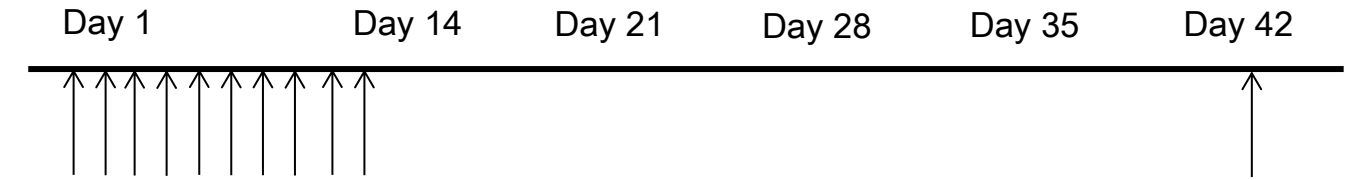
Gene/gene set overlap matrix

Gene Symbol	Gene Description
SLC5A7	solute carrier family 5 (choline transporter), member 7
SLC18A3	solute carrier family 18 (vesicular acetylcholine), member 3
SLC6A5	solute carrier family 6 (neurotransmitter transporter, glycine), member 5
SV2C	synaptic vesicle glycoprotein 2C
S100A10	S100 calcium binding protein A10
FAM111A	family with sequence similarity 111, member A
PRPH	peripherin



(Kim et al., 1st revision)

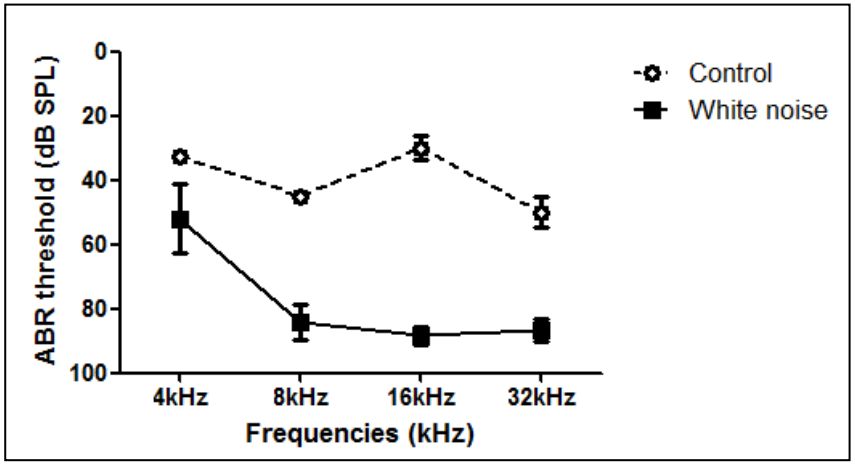
Noise-Induced Hearing Loss: Animal exposures



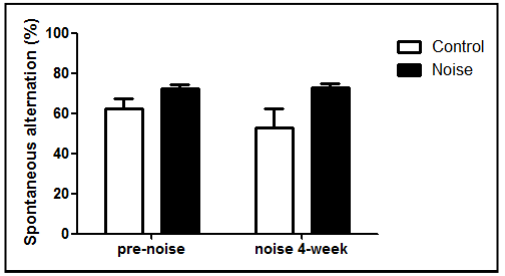
White noise (2-20kHz), 115 dB SPL, 4 hours/per day (n = 10)
Control (n = 10)

ABR, Y-maze, Novelty
Sacrifice

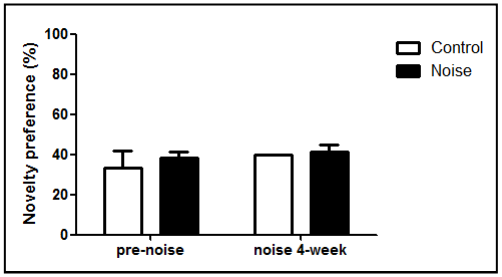
ABR



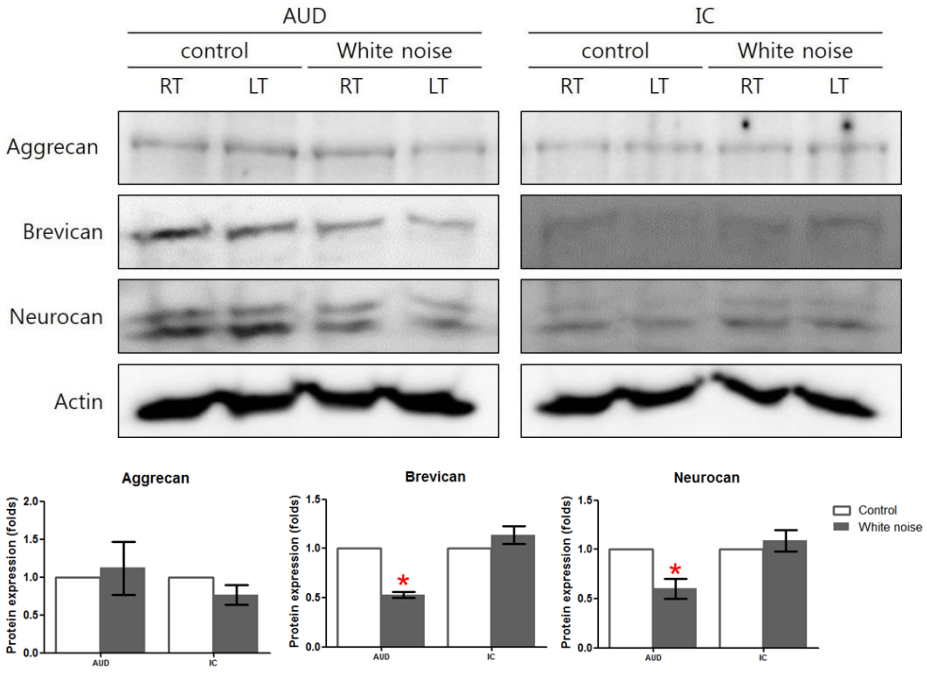
Y-maze

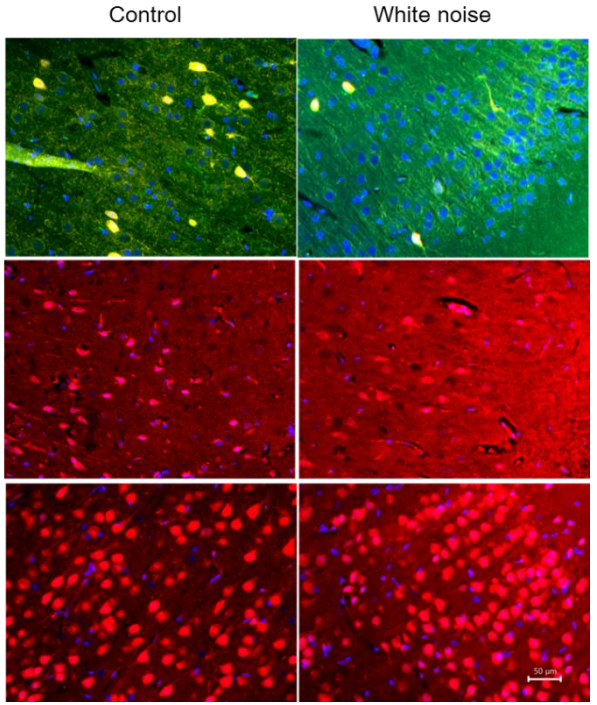


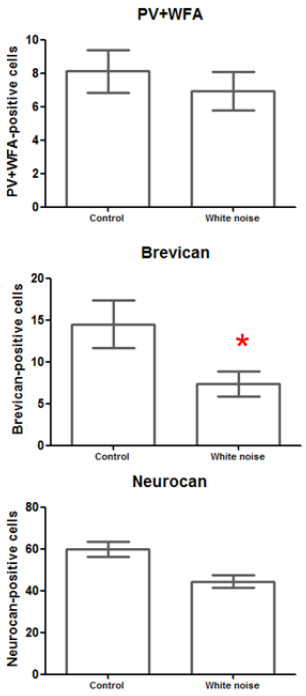
Novelty



Noise-Induced Hearing Loss: PNNs

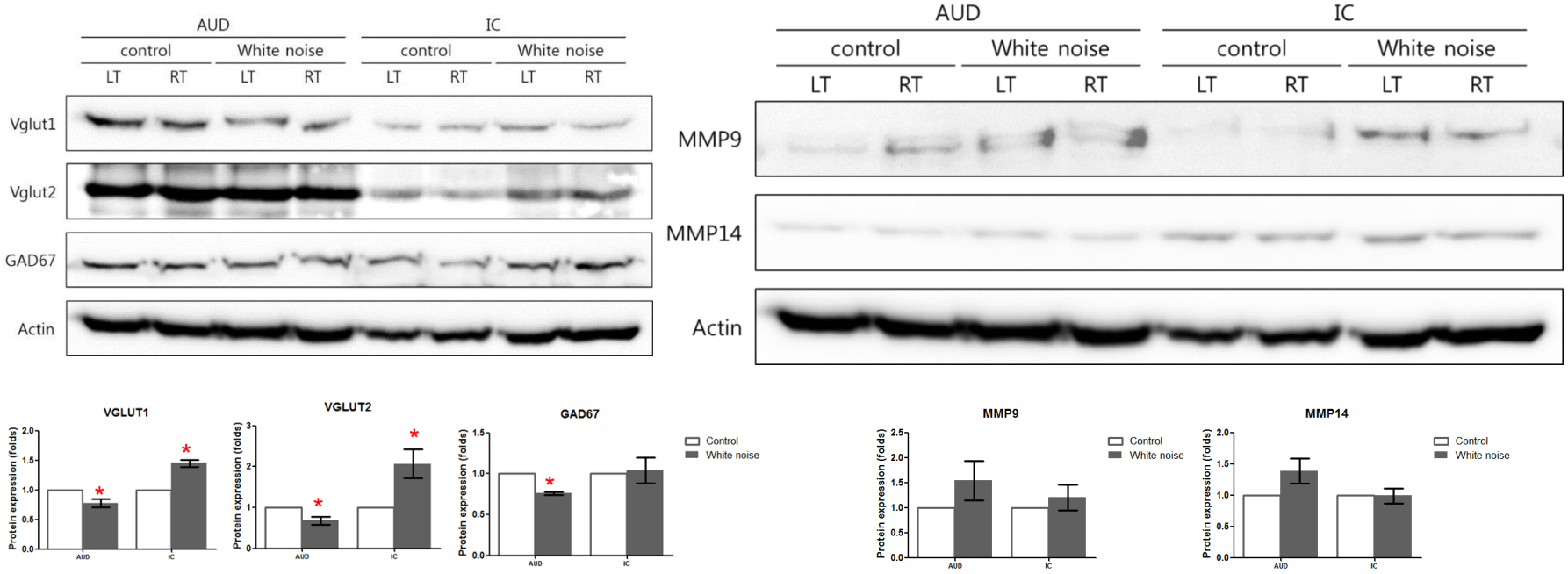






- Brevican and neurocan expressions were decreased in the noise group.
- Brevican was reported to have a role in fast synaptic transmission, which was supported by a knockout mouse study. *(Sonntag, M. et al.,BMC biology, 2018)*
- Neurocan is a component of PNNs and inhibits neuroplastic changes by interacting with the dendritic receptors of semaphoring 3F and neural cell adhesion molecule/ephrin type I receptor 3. *(Sullivan, C.S. et al., Sci Rep, 2018)*

Noise-Induced Hearing Loss: vesicular transporters and matrix metalloproteinases



- The glutamatergic neural transmission involving VGLUT1 and VGLUT2 were decreased 1 month after noise exposure in this study.
- VGLUT2 was increased in the inferior colliculus.
- The degradative enzymes of MMP9 was increased in A1.

(Kim et al., submitted)

Noise-Induced Hearing Loss: presynaptic vesicular transporters

- VGLUT1 expression is high in A1, and increased upto P21 in mice.

(Troy A.Hackett et al., Brain Struc Funct, 2016)

- Both VGLUT1 and VGAT expressions were decreased in the ventral cochlear nucleus of age-related hearing loss rats.

(Juan C.Alvarado et al., Front Aging Neurosci, 2014)

The decrease of VGLUT1 imply the reduced glutamergic transmission in noise-induced hearing loss.

- The cochlear insult increased the VGLUT2 expression in the dorsal cochlear nucleus. *(A.N.Heeringa et al., Neuroscience, 2016)*
- The sources of VGLUT2 terminals in the IC are somatosensory and vestibular terminals, while those of VGLUT1 is only in the ipsilateral A1.

(Tetsufumi Ito et al., Front Neuroanat, 2010)

The increase of VGLUT2 in the inferior colliculus indicated the cross-modal compensation which could be related with tinnitus.

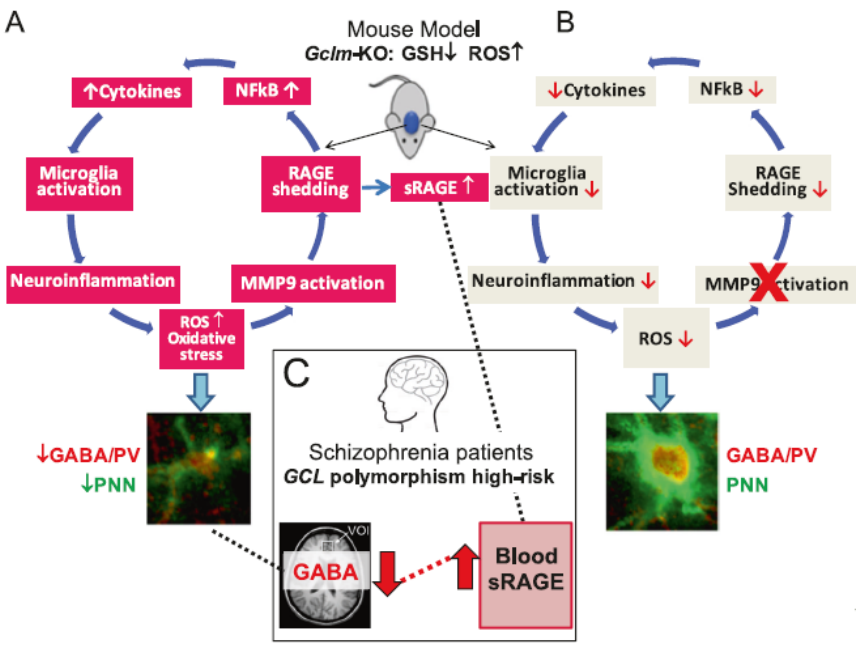
Noise-Induced Hearing Loss: MMP9 and RAGE

- The MMP9 expression was increased in the A1 in the age-related hearing loss model. *(Yang Dong et al., Mol Med Rep, 2018)*
- Acute brain injury in meningitis up-regulated the MMP9 activities and the high MMP9 level was related with the hearing loss.

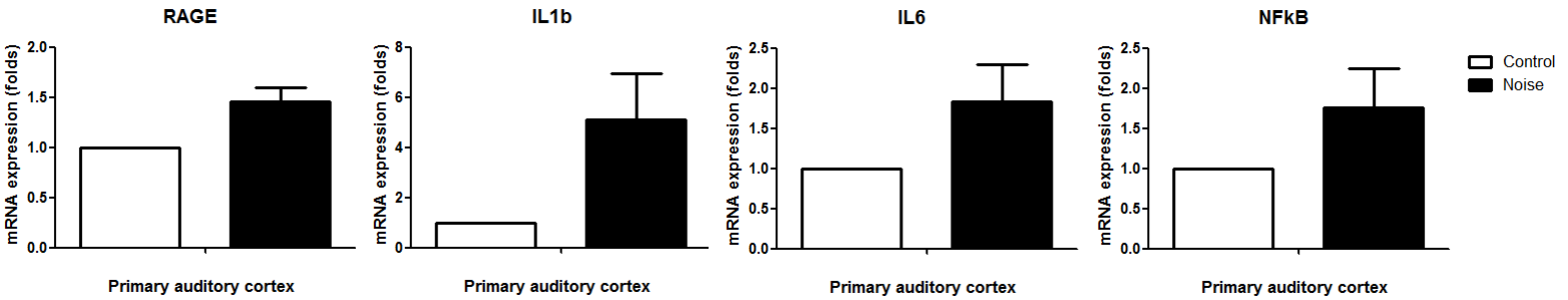
(Lukas Muri et al., J Neuroinflammation, 2018)

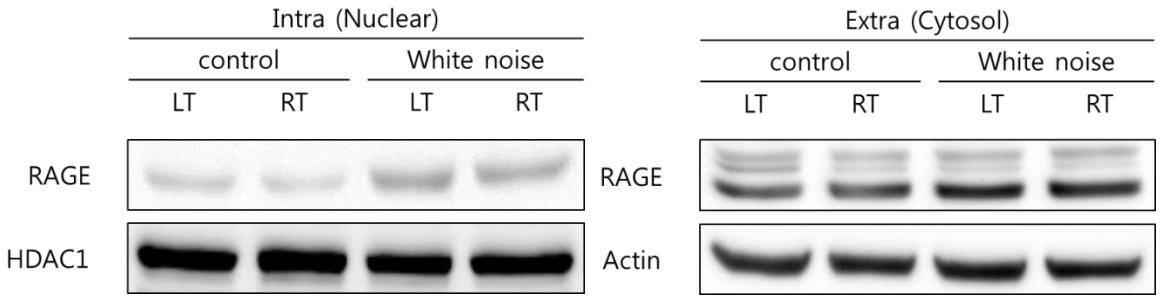
- The MMP9 activation leads to the shedding of receptor for advanced glycation end-products (RAGE), and secretion of inflammatory cytokines, which accentuate the decrease of PNNs.

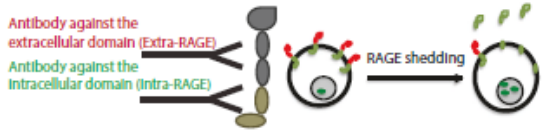
(Daniella Dwir et al., Mol Psychiatry, 2019)

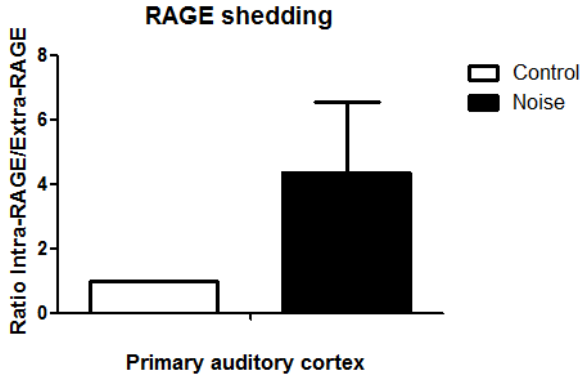


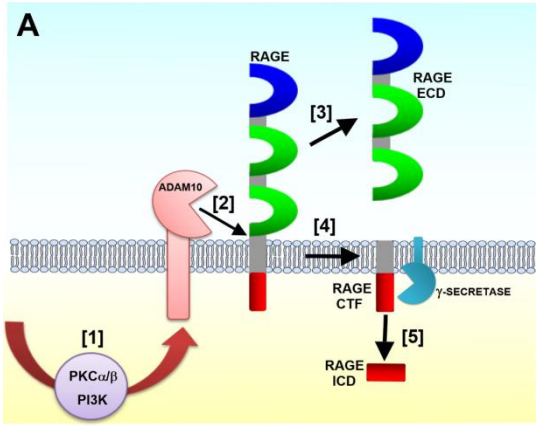
Noise-Induced Hearing Loss: RAGE shedding











(Braley A et al. J Biol Chem. 2016)

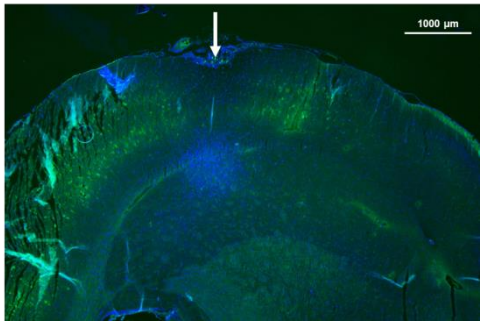
Conclusion

- Cortical reorganization following hearing loss:
  - Single-sided deaf increased the presynaptic transporters and components of PNNs in ipsilateral (non-dominant) side of A1.
  - On the other hands, the contralateral (dominant) side of A1 increased the degradative changes of PNNs.

- Neural degeneration following hearing loss:
  - The noise-induced hearing loss resulted in the decreased PNNs accompanied with decrease of presynaptic excitatory transmitter in the A1.
  - The brevican and less amounts of neurocan were decreased in the noise-induced hearing loss rats, which was probably mediated by the increased level of MMP9 in the A1.

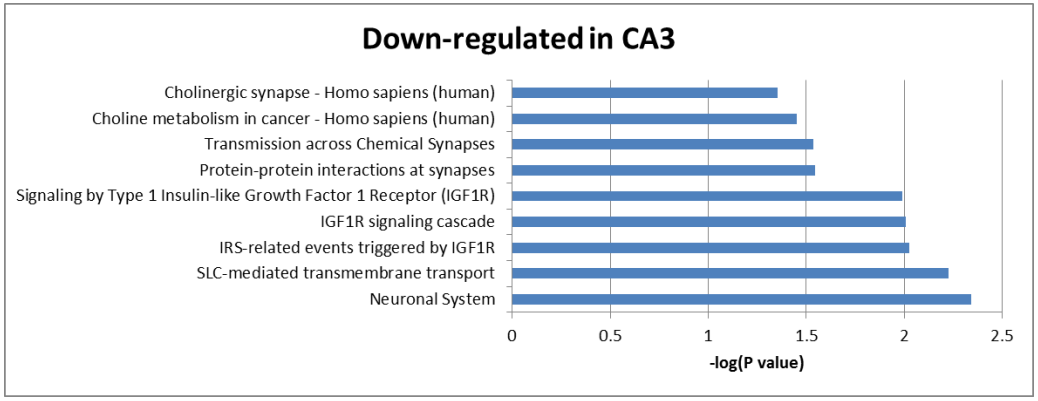
Future or Ongoing Studies

NBN+ChABC Ipsilateral



- **Cortical reorganization following hearing loss:**
  - Restoration of neural plasticity
  - Degradation of PNNs using chondroitinase ABC.

- **Neural degeneration following hearing loss:**
  - Prevention of PNNs degradation
  - MMP9 or ADAM10/secretase inhibitors
- Molecular mechanisms for the impact of hearing loss on cognitive function.



Gene symbol	Gene description
SYT9	synaptotagmin 9
SLITRK6	SLIT and NTRK like family member 6
KCNJ16	potassium voltage-gated channel subfamily J member 16
SLC5A7	solute carrier family 5 member 7
CHRNA3	cholinergic receptor nicotinic alpha 3 subunit
SLC4A5	solute carrier family 4 member 5
SLC40A1	solute carrier family 40 member 1
SLC5A3	solute carrier family 5 member 3
IGF2	insulin like growth factor 2
KL	klotho
KCNJ16	potassium voltage-gated channel subfamily J member 16
CHRNA3	cholinergic receptor nicotinic alpha 3 subunit

Thank you for attention!