Auditory Research Group
Southern Illinois University
School of Medicine

Aging in Sensory CNS Pathways:

- Decreases Ascending Signal Clarity
- Engages Top-Down Cognitive and Attentional Mechanisms
- Treatable biomarker for cognitive impairment?

Is age-related hearing loss associated with an increased risk for cognitive decline, cognitive impairment, and dementia?

From: Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia: A Systematic Review and Meta-analysis **(Loughrey et al., 2018)**

- A systematic meta-analysis of 36 epidemiologic studies and 20,264 unique participants.
- Age-related hearing loss (ARHL) was significantly associated with a decline in all main cognitive domains and with increased risk for cognitive impairment and incident dementia.
- Increased risk for Alzheimer disease and vascular dementia was not significant.
- ARHL precedes the onset of clinical dementia by 5 to 10 years and may serve as a biomarker.
- These findings offer a possible pathway to modify clinical outcomes.

Does a Degraded Up-Stream Code Increase Use of Top-down Resources

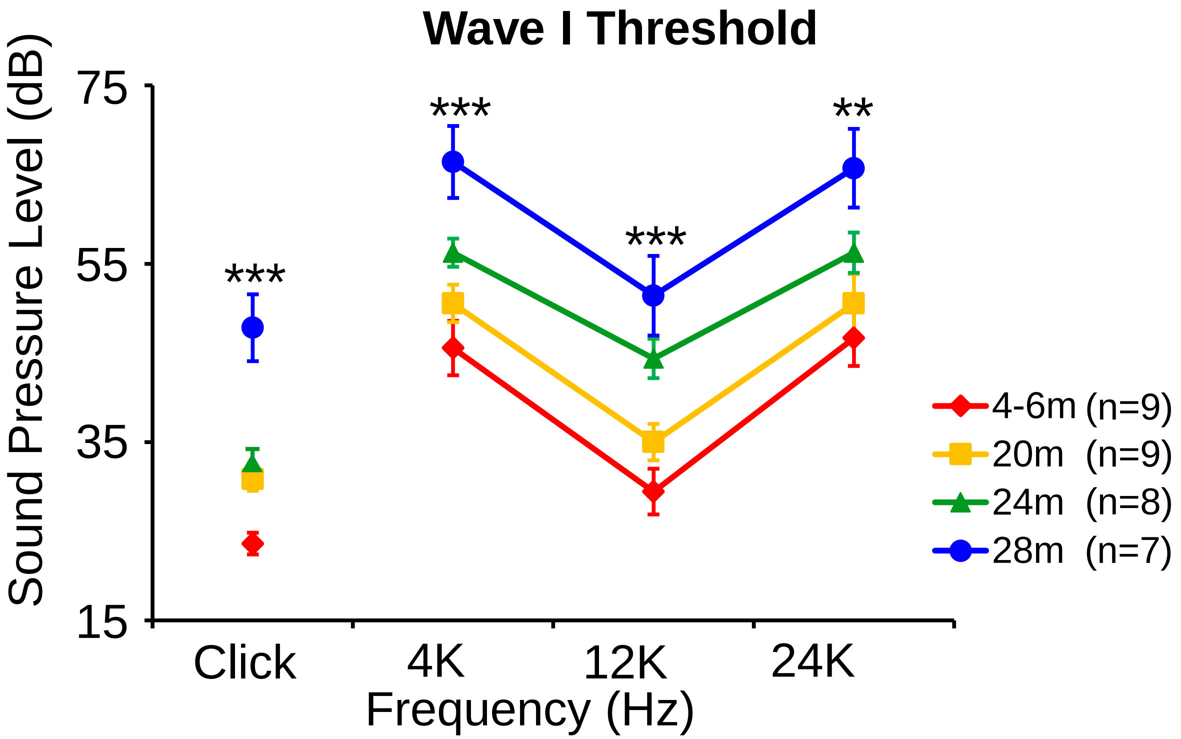
- Even moderate hearing loss can significantly impair quality of life, potentially leading to social withdrawal and depression.
- Human show large variations in age-related loss of peripheral input that only partially correlates with the aged-related loss of speech understanding.
- These deficits are more pronounced when attention is challenged.
- Adaptation to repetitive stimuli is a hallmark of ascending sensory systems.
- Older humans increase their use of top-down cues to disambiguate corrupted ascending communication sounds.
- **Can we examine this in an animal model?**

- Hypothesis
  - An age-related decrease in input to central auditory structures will result in maladaptive changes at inhibitory synapses throughout the central auditory pathway.
- Impact
  - Increased jitter in the bottom-up temporal code.
  - Increased use of top-down resources
- Approach
  - Examine markers of inhibitory neurotransmission (glycine and GABA) in rat models of aging.
  - Examine impact of aging on responses to temporally complex acoustic stimuli in auditory thalamus (MGB).
- Potential Clinical Benefit
  - Identity of a novel receptor target(s) in aged circuits offers the possibility of drugs and/or behavioral therapy to improve speech understanding.

FBN Rat Model of Aging

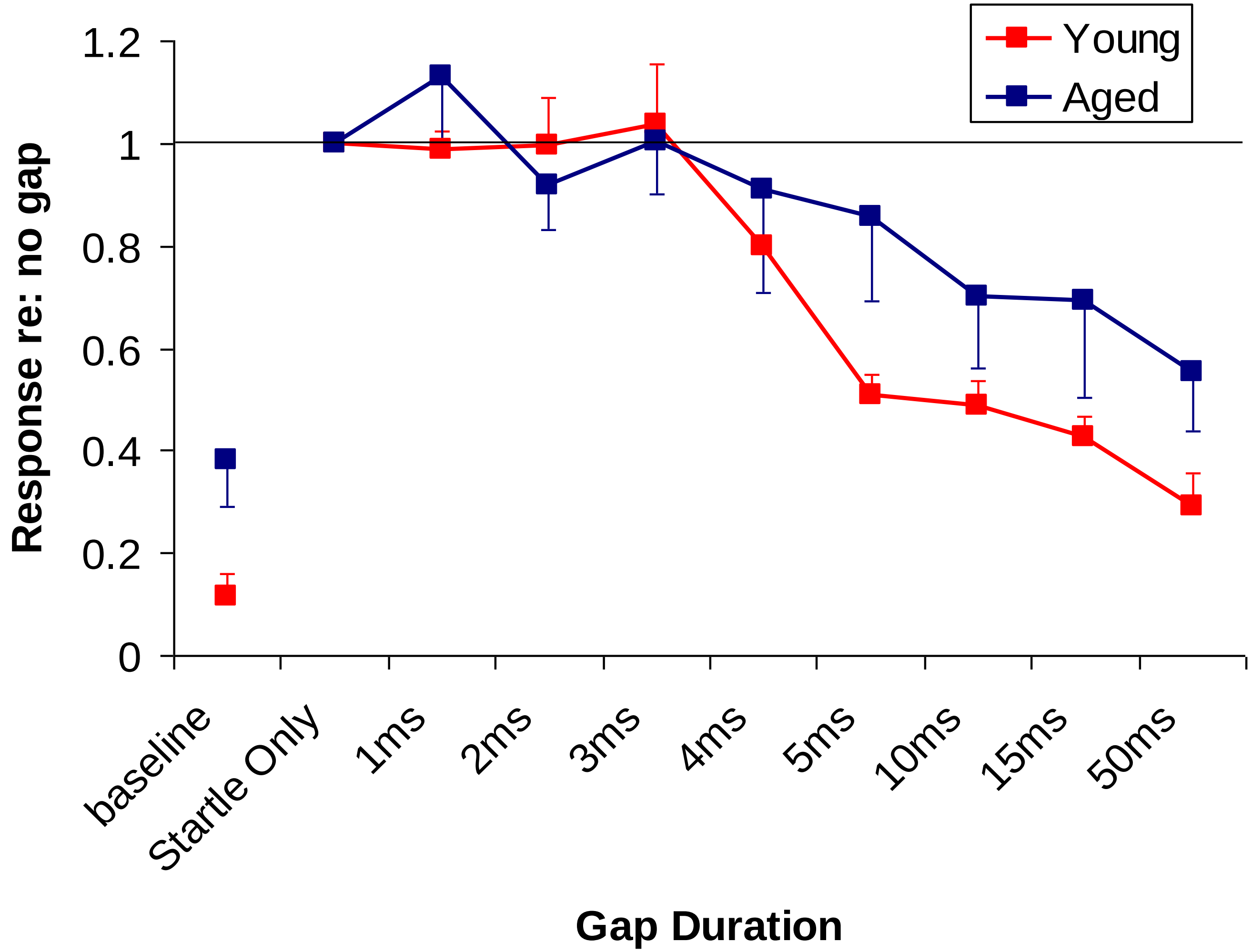
F344xBN F1=FBN:

Median Life Span: 36mos.   Max. Life Span: 44mos.



Cai et al., 2018

Aging Degrades the Temporal Code

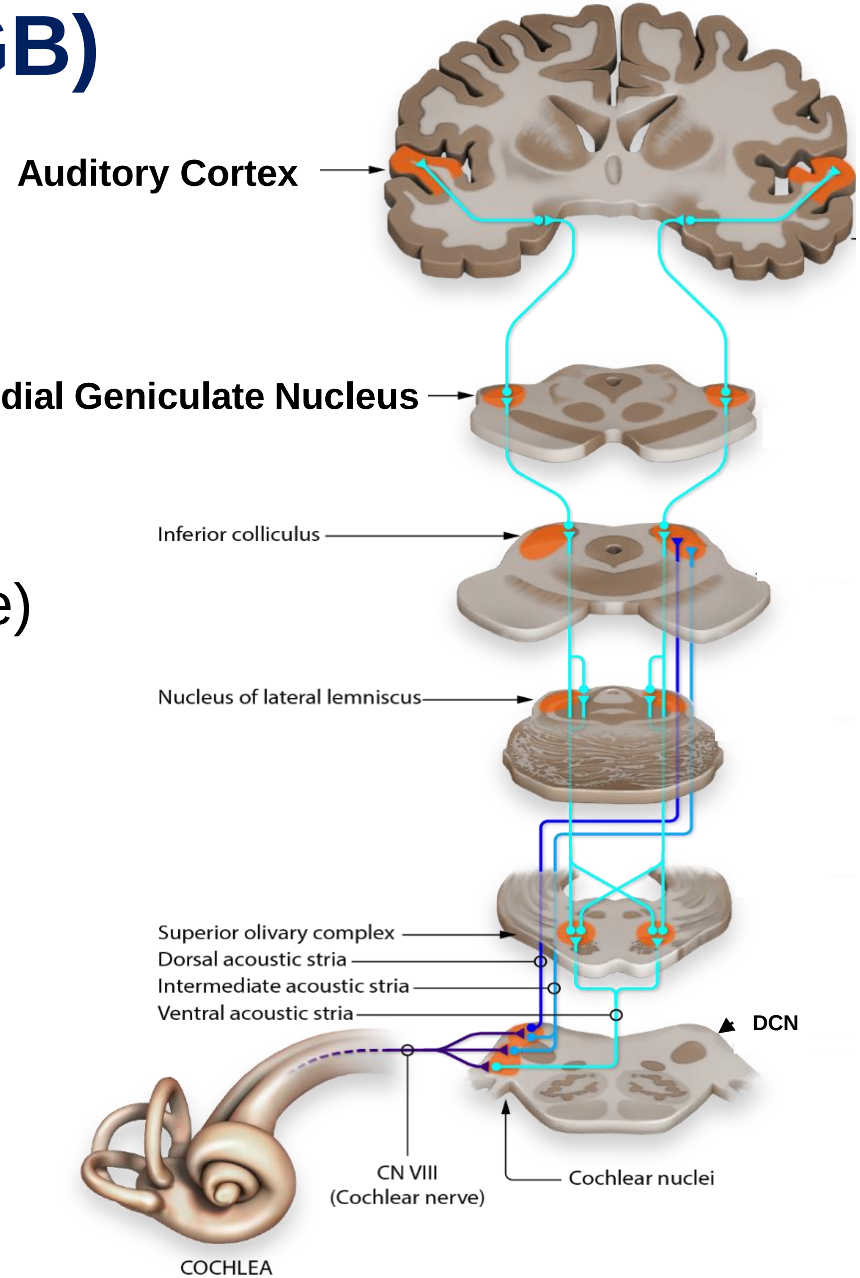


FBN rats: Young 4-6 months old (n=8); Aged 32-38 months old (n=8).

Human-Strouse et al.,1998;Schneider and Hamstra, 1999; **Mouse**-Bartz et al., 2002; **Gerbil**-Hamann et al.,2004: **Rat**-Wang et al., 2009a

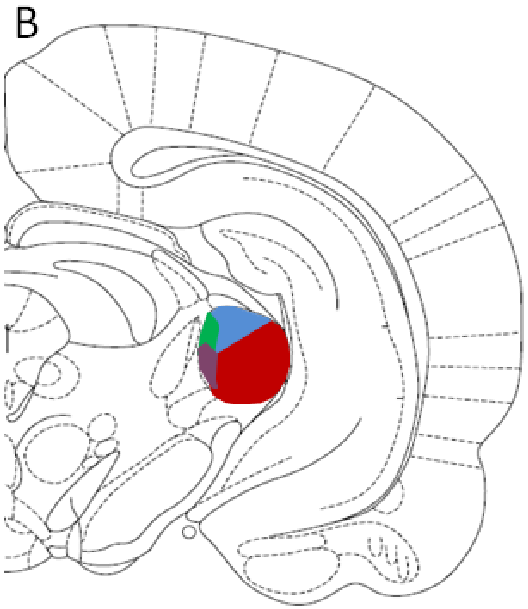
Aging and Attention in Auditory Thalamus (MGB)

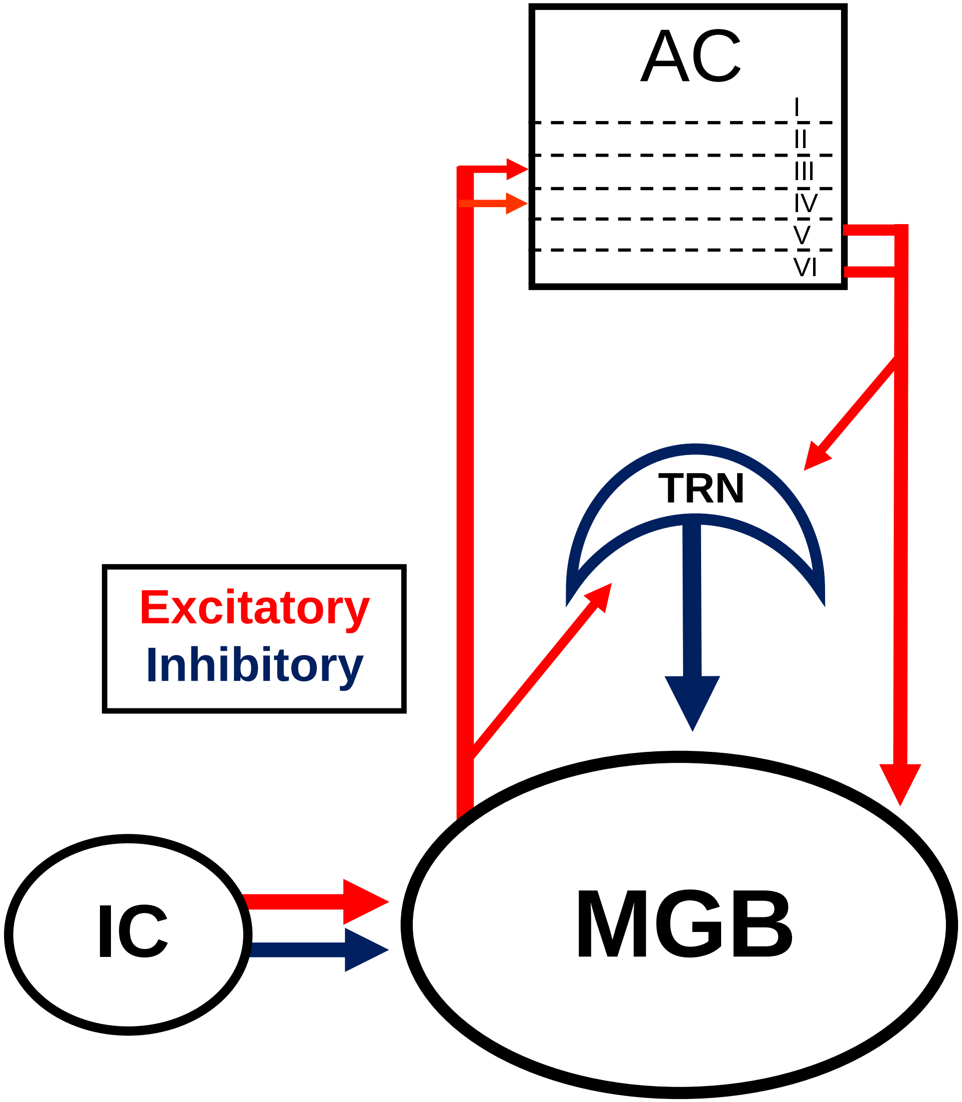
- Relays Acoustic Information to Cortex
- Temporal Processing of Acoustic Information
    - Speech Processing (sparse code)
- Gating of Acoustic Information/**Attention**
    - Top-down bottom-up integration



Modified from Peelle and Wingfield, 2016

Medial Geniculate Body





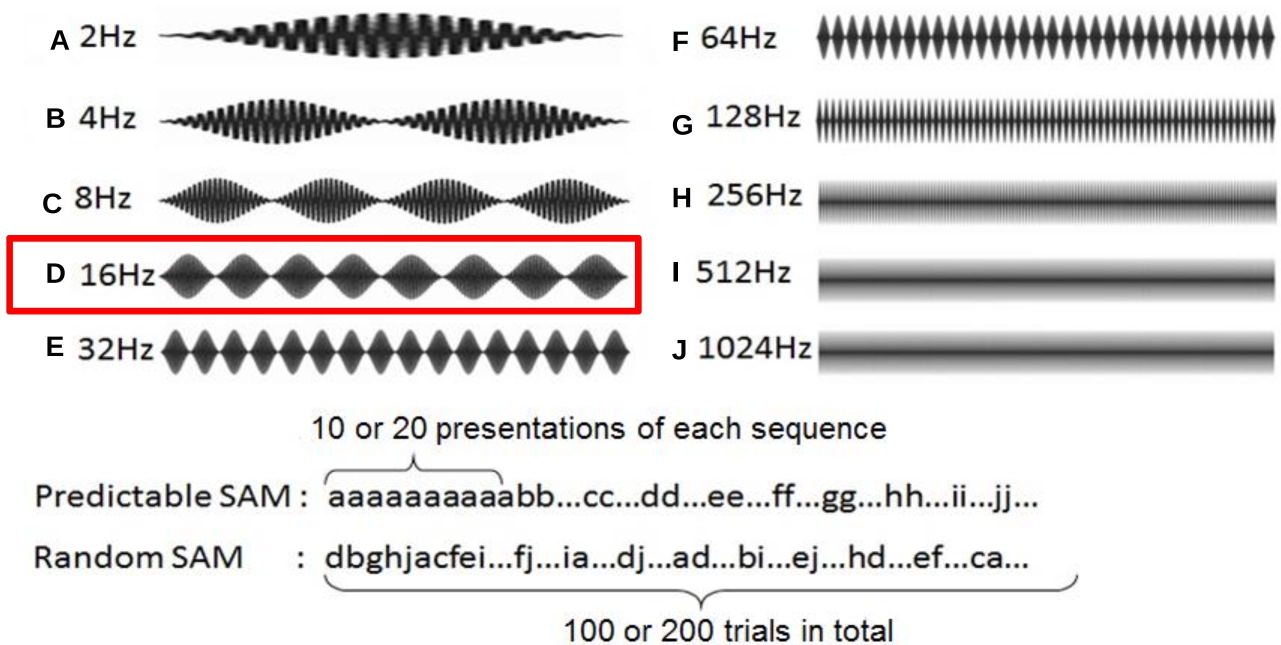
- Ventral Division (Primary/Lemniscal)
- Dorsal Division (Secondary/Non-Lemniscal)
- Medial Division

AC: Auditory Cortex
MGB: Medial Geniculate Body
IC: Inferior Colliculus
TRN: Thalamic Reticular Nucleus

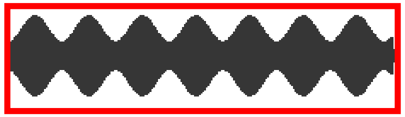
Paxinos & Watson, 1998

Stimulus Set Presented to Rat While Recording Single-units in Medial Geniculate Body

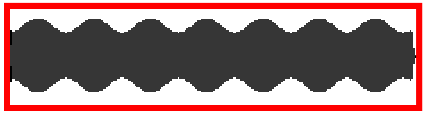
100 % Modulation Depth Across Modulation Frequencies Examined



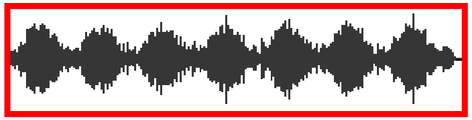
Examples of Less Salient SAM



50 % Modulation Depth SAM



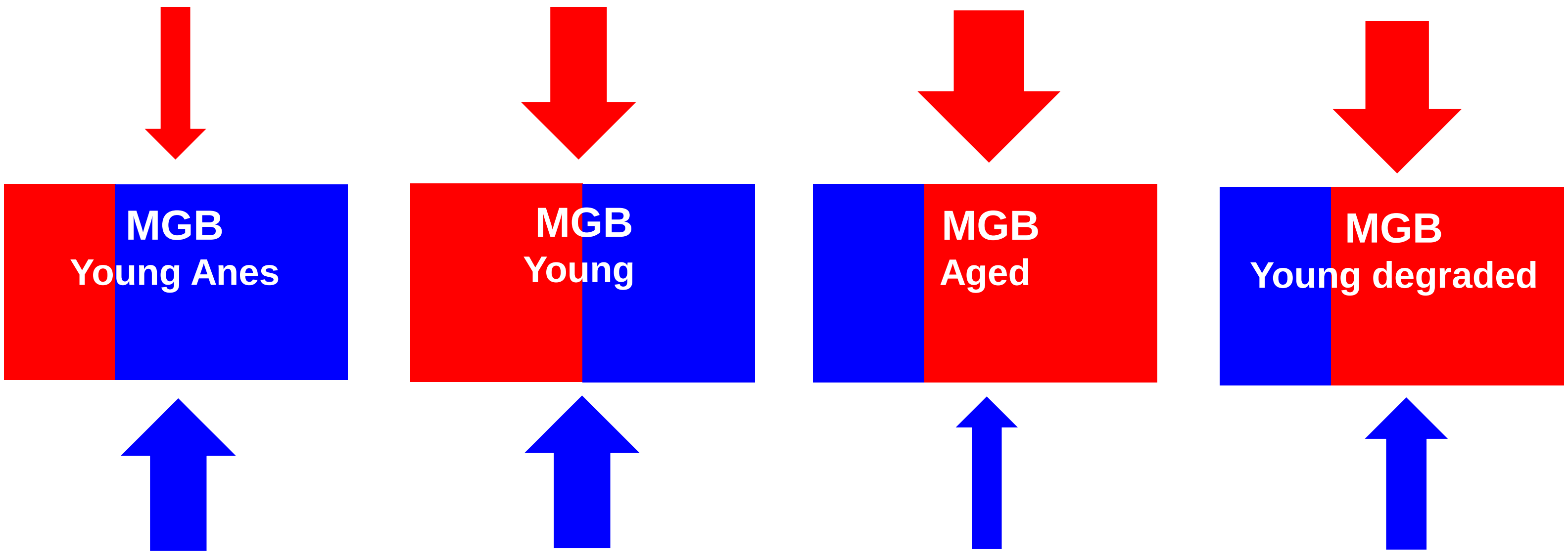
25 % Modulation Depth SAM



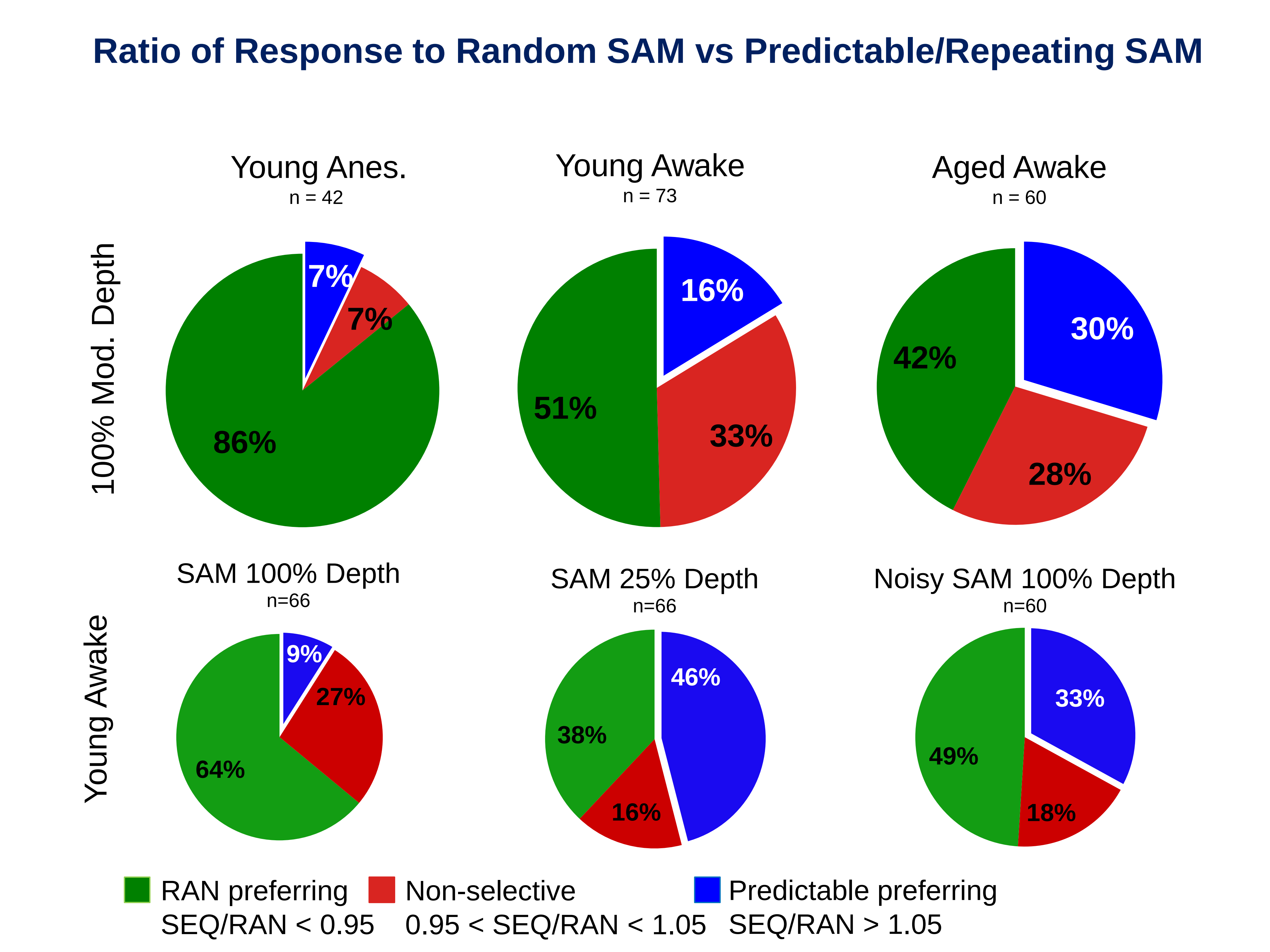
Noisy 100% Depth SAM

Coding of Auditory Information is Shaped by Ascending/Bottom-up and Descending/Top-down Influences.

Top down modulation
Prefer Predictable-Sequential

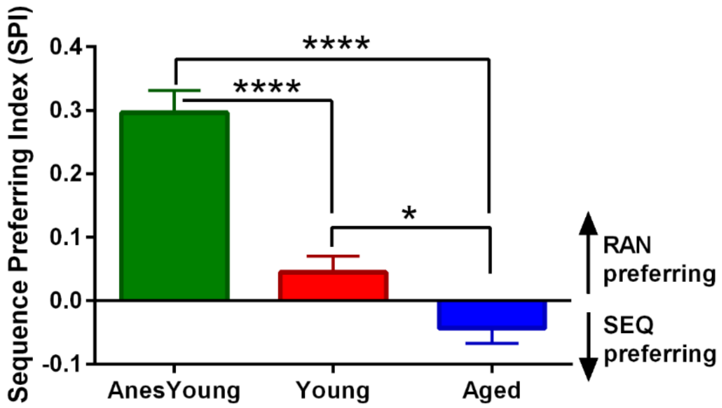


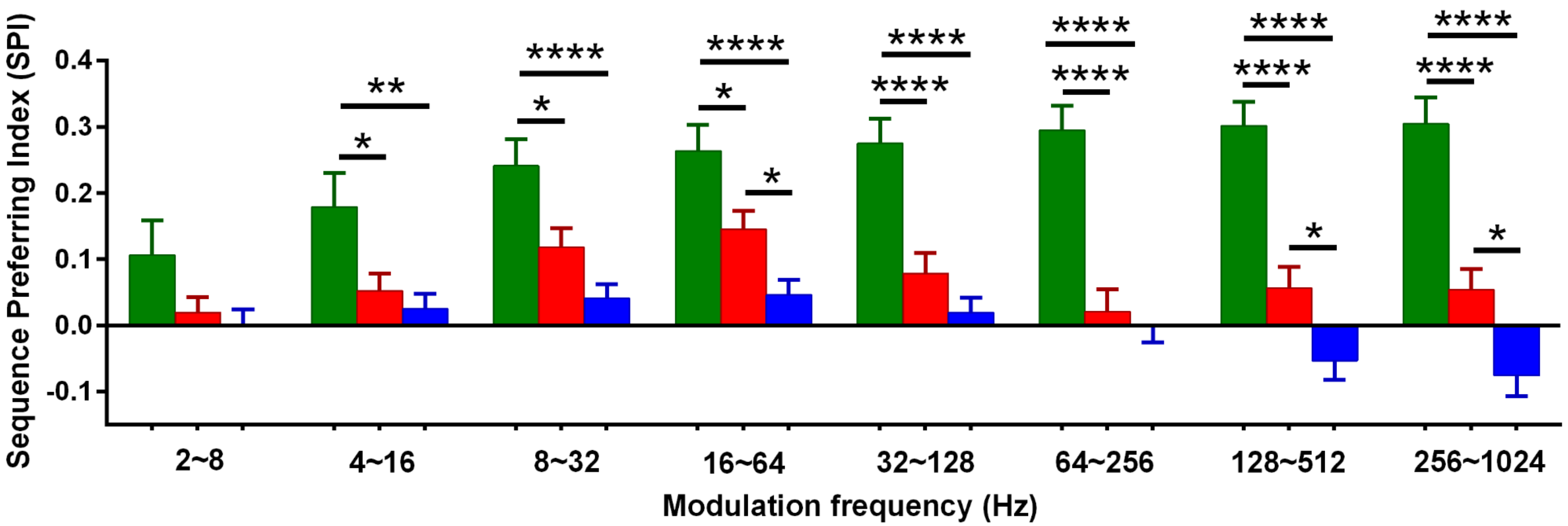
Bottom up input
Prefer Random



Ratio of Response to Random SAM vs Predictable/Repeating SAM
Young Anes.
n = 42
Young Awake
n = 73
Aged Awake
n = 60
100% Mod. Depth
7%
7%
86%
16%
33%
51%
30%
28%
42%
SAM 100% Depth
n=66
SAM 25% Depth
n=66
Noisy SAM 100% Depth
n=60
Young Awake
9%
27%
64%
46%
16%
38%
33%
18%
49%
RAN preferring
SEQ/RAN < 0.95
Non-selective
0.95 < SEQ/RAN < 1.05
Predictable preferring
SEQ/RAN > 1.05

Sequence Preference Index: Aging and Anesthesia



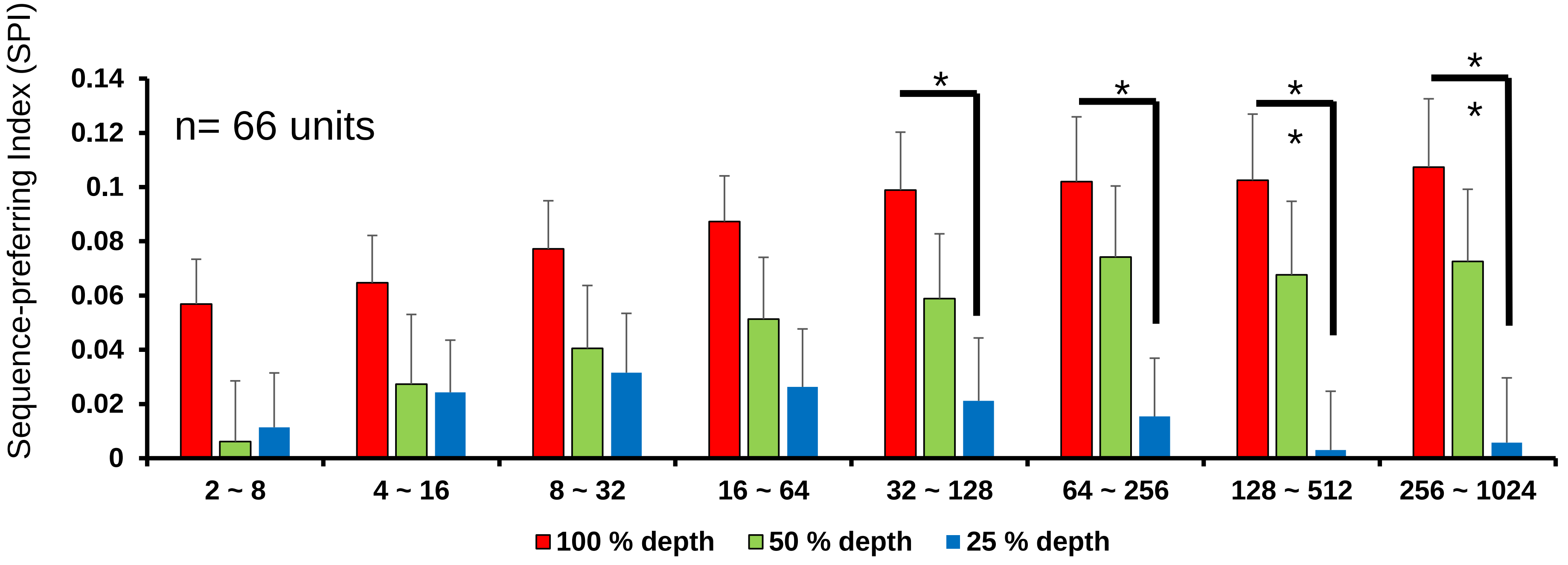


Sequence-preferring index: SPI = $[(AUC_{RAN} - AUC_{SEQ})/(AUC_{RAN} + AUC_{SEQ})]$

modified from Lumani and Zhang, 2010

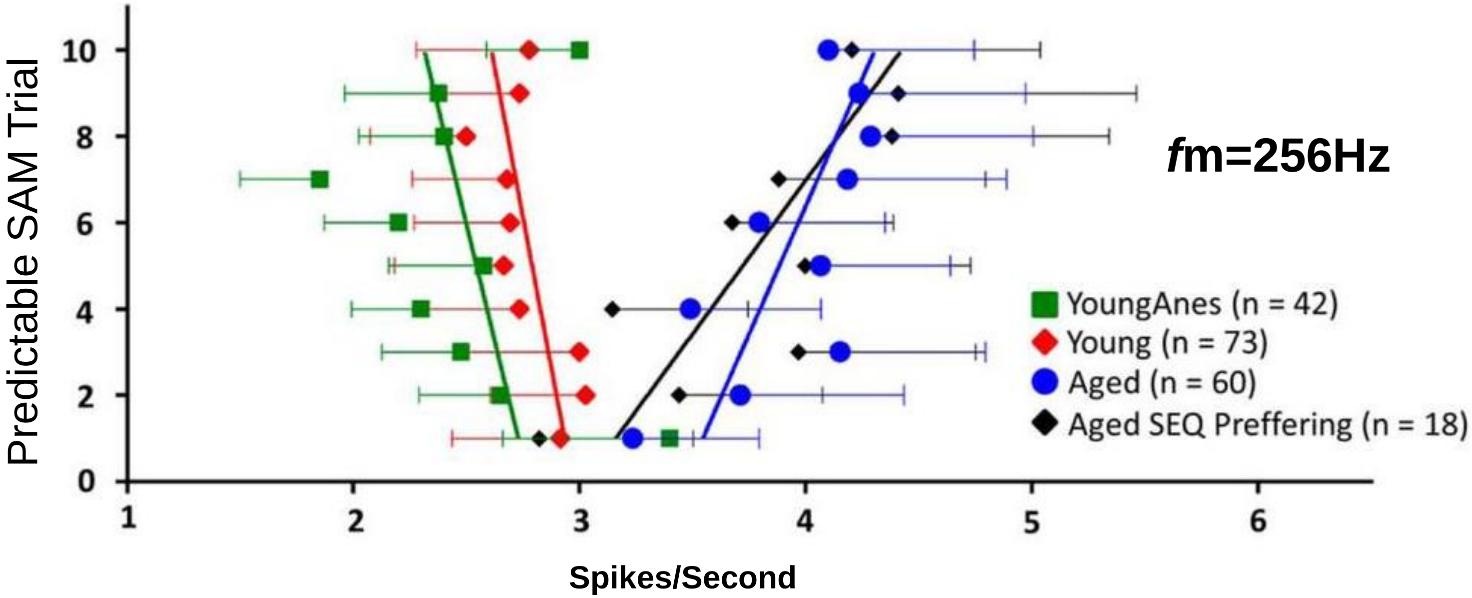
Cai et al.,2016, *J. Neurosci.*

SPI: Less Salient Modulated Stimuli Across Modulation Frequency



Sequence-preferring index: SPI = $[(AUC_{RAN} - AUC_{SEQ})/(AUC_{RAN} + AUC_{SEQ})]$, modified from Lumani and Zhang, 2010

Trial-by-trial response analysis to Predictable SAM at a Single f_{mod}



Cai et al.,2016, *J. Neurosci.*

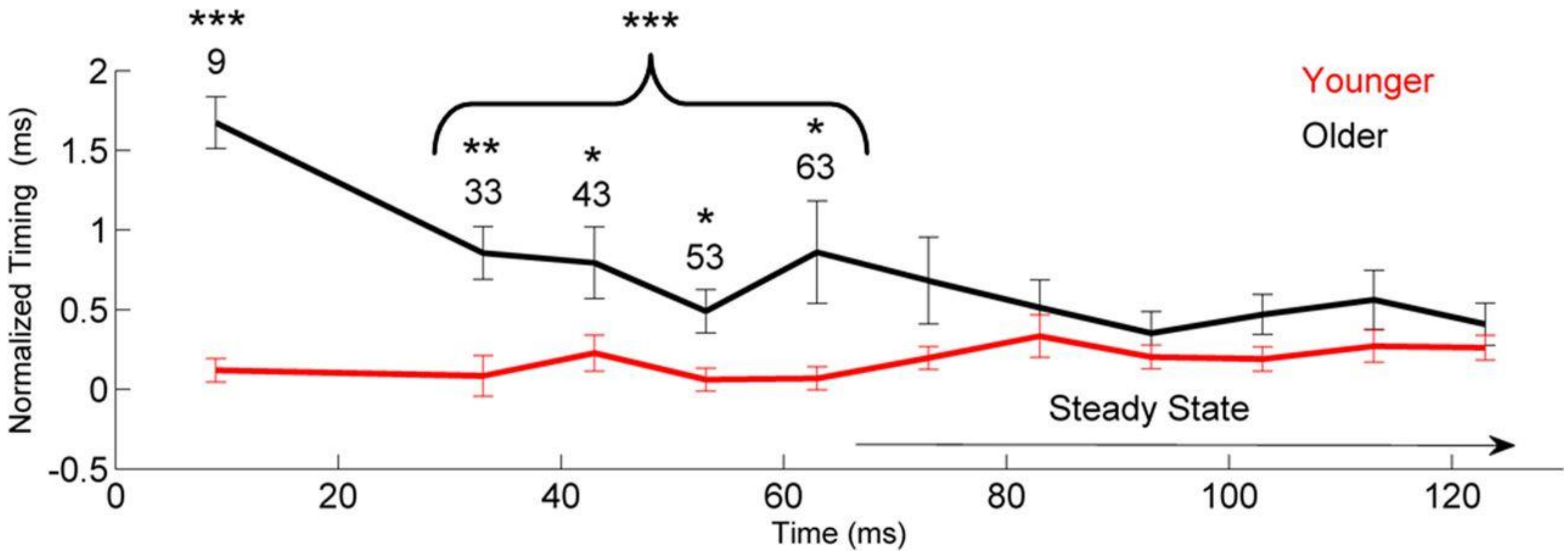
Conclusions Aging and Predictive Top-Down Processing

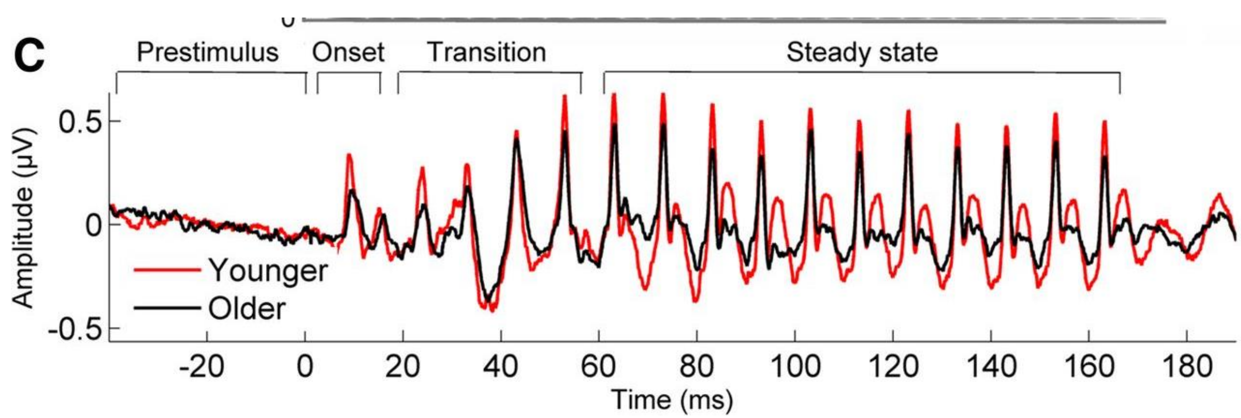
- Auditory neurons recorded from aged animals appear to selectively “expect” repeated or predictable modulated signals.
- Auditory neurons from young animals show increased preference for degraded predictable SAM stimuli.
- **Older individuals engage cognitive/memory/attentive resources to disambiguate speech in complex acoustic environments.**
- **Adequate Speech understanding requires functioning cognitive/memory/attentive mechanisms!**

What Can Be Done to Ameliorate Age-Related Loss of Speech Understanding and the Possible Link to Cognitive Decline?

- Can hearing aids reverse central auditory changes?
- Can psychoacoustic training reverse central auditory changes?
- Do these strategies work?
  - Human
  - Animal model

FFR-Neural Delays in the Aging Population.





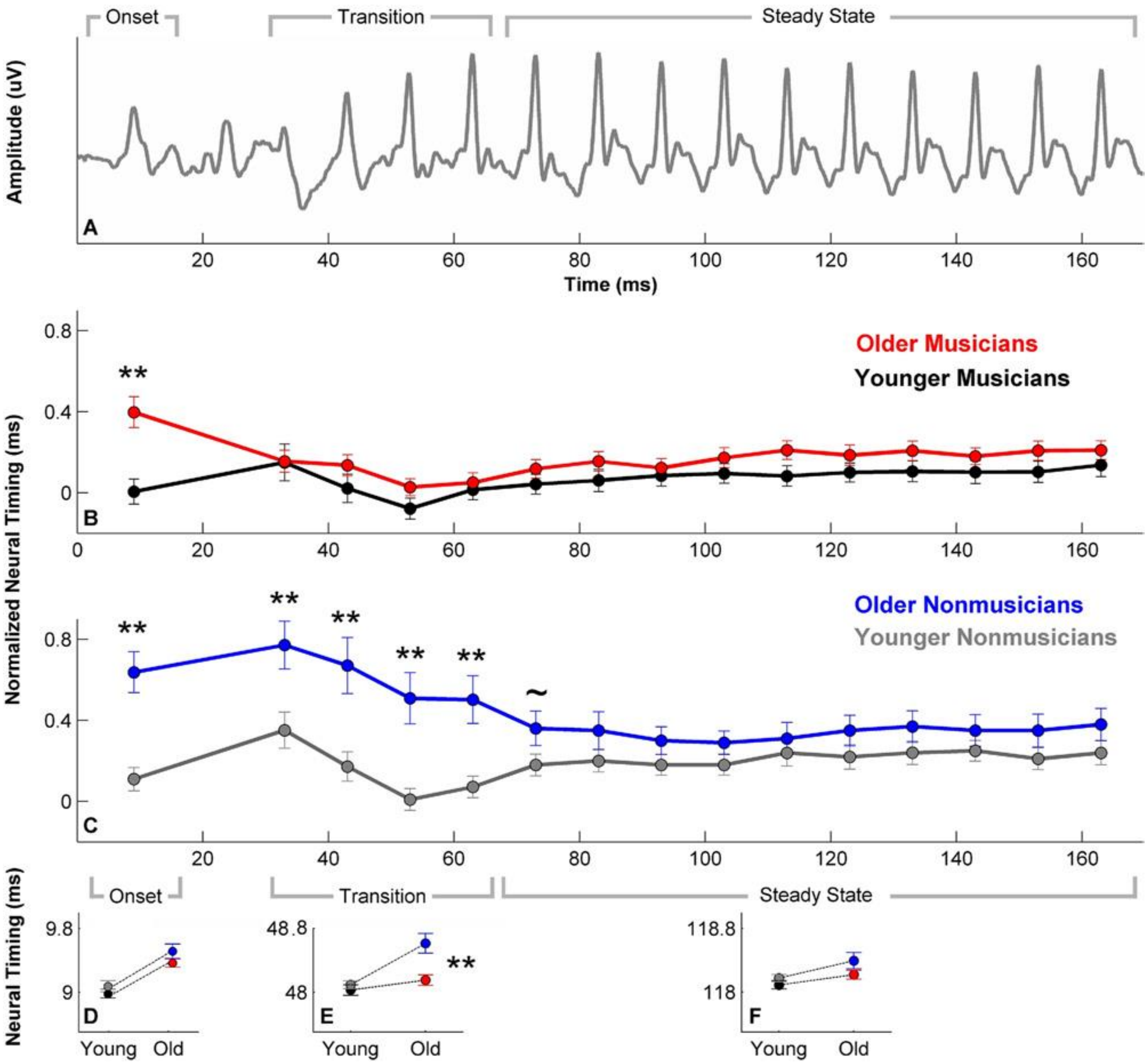
[da]

N= 17 (18–30 years old) & 17 (60–67 years old)

Age-related shift in neural response timing for onset and transition but not for the steady state portion of **“da”**

Anderson et al. J. Neurosci. 2012;32:14156-14164

Musical Experience Offsets Age-related Delays in Neural Timing



[da]

Parbery-Clark et al.,2012

Some Final Thoughts

- Human studies show that age-related degraded ascending acoustic information can be partially disambiguated/clarified by increasing use of top-down cognitive resources.
- Some version of this can be studied in an animal model.
- Unfortunately, human studies suggest that the elderly require increased attentional effort to best engage top-down resources.
- Present studies suggest that cholinergic attentional circuits positioned to refine top-down coding of acoustic information are negatively impacted by aging.