Paper discussion

Meeting Fundamental neuromodulation

4th September 2019

Stijn Michielse PhD

GitHub

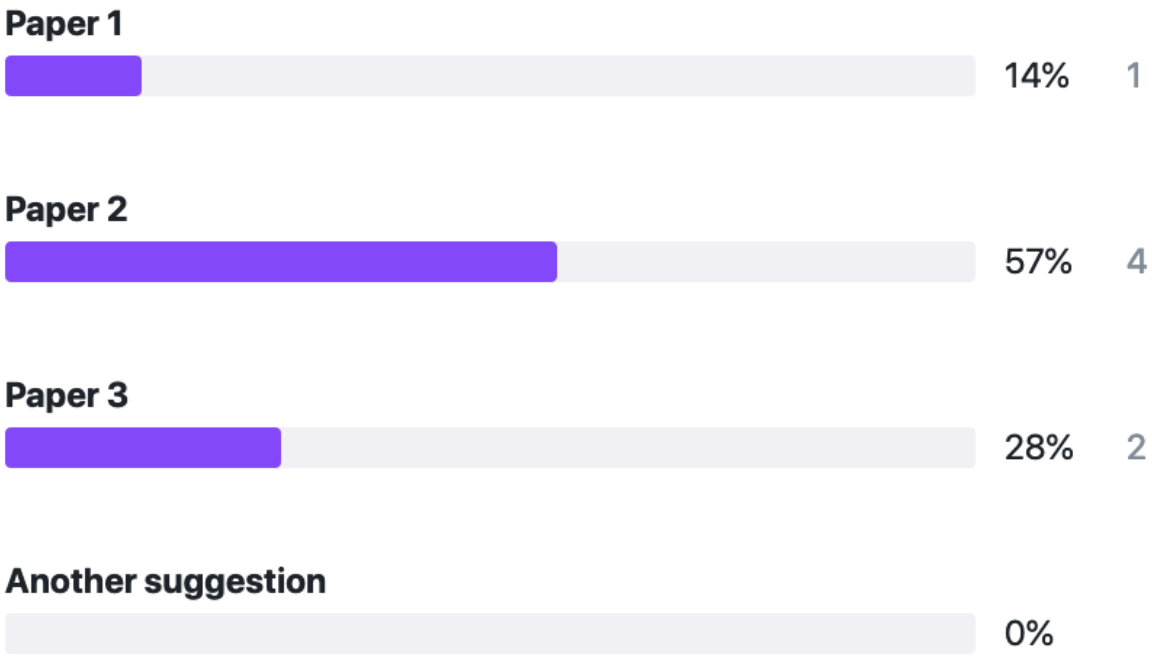
- Git = version control system
- Sharing code
- Repositories
- Contribution and collaboration
- Transparency of research

- Mascot; octacat

Why GitHub?

- Documentation of research
- Markdown; write code → create manuscript
- Track changes, version control
- Compatibility between platforms

Voting



Paper 2: *Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus*

frontiers in
SYSTEMS NEUROSCIENCE

REVIEW ARTICLE
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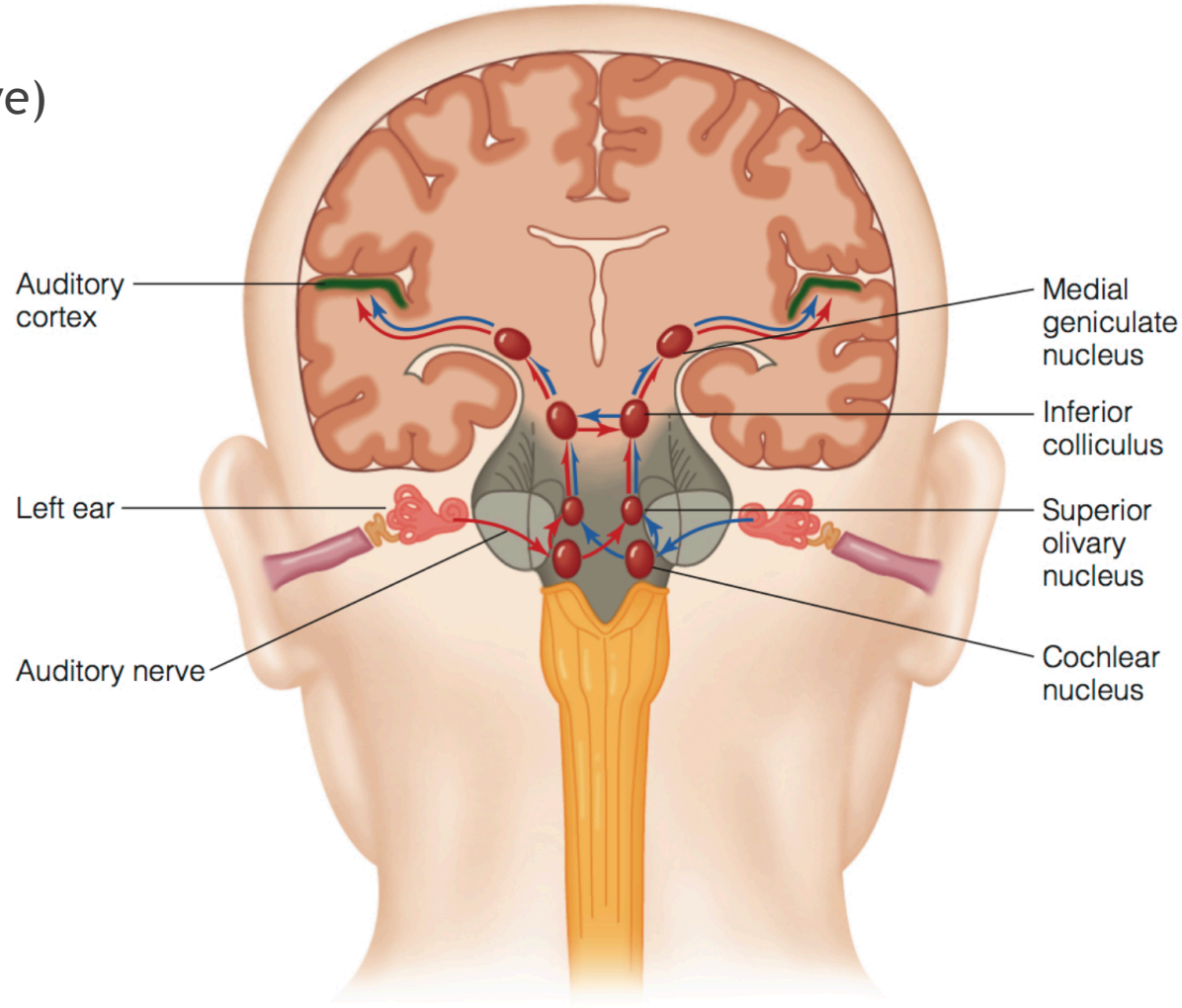
Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus

Berthold Langguth[1,2]*, Martin Schecklmann[1,2], Astrid Lehner[1,2], Michael Landgrebe[1,2], Timm Benjamin Poeppl[1,2], Peter Michal Kreuzer[1,2], Winfried Schlee[3], Nathan Weisz[4], Sven Vanneste[5] and Dirk De Ridder[5]

- Published in 2012 by a research group located in Regensburg, Germany
- 42 citations
- Review paper on Neuroimaging and Neuromodulation in tinnitus
- Tinnitus = perception of noise or ringing in the ears
- Causes; age related (presbycusis), exposure to loud noise, neuroma
- Origin in the auditory nerve or related pathway

Cochlear nerve

- Origin; vestibulocochlear nerve (8th cranial nerve)
- 30,000 nerve fibers
- Transsection of the nerve → tinnitus preserved
- Central auditory system



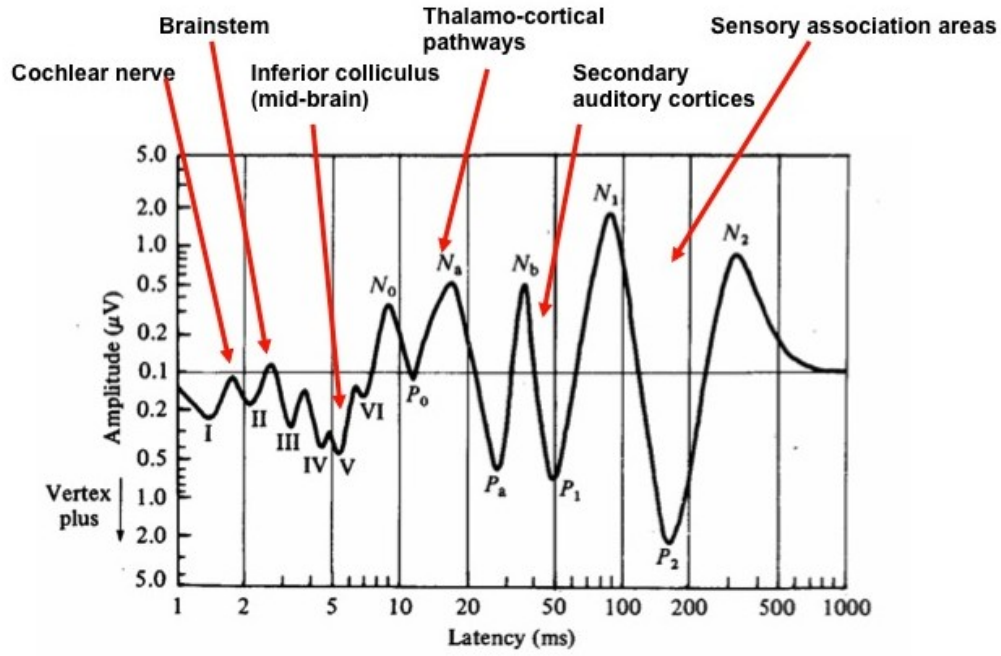
Functional pathways involved in tinnitus

- Dorsolateral prefrontal cortex
- Orbitofrontal cortex
- Anterior cingulate
- Subgenual cingulate
- Posterior cingulate
- Parietal cortex
- Amygdala
- Hippocampus
- Parahippocampus
- Cerebellum

- Fairly broad and unspecific
- Correlational approach
  - No causality
- Attention, memory, emotion

Auditory pathways

- PET studies
  - Increased blood flow in auditory structures
  - In unilateral tinnitus → contralateral activation affected
  - In lateral tinnitus → increased activation in left hemisphere (hallucinations?)
- MEG and EEG
  - Temporal cortex → reduction of alpha activity
    - increase of slow wave and gamma activity
  - Auditory evoked potentials → inconclusive
  - Altered somatosensory input



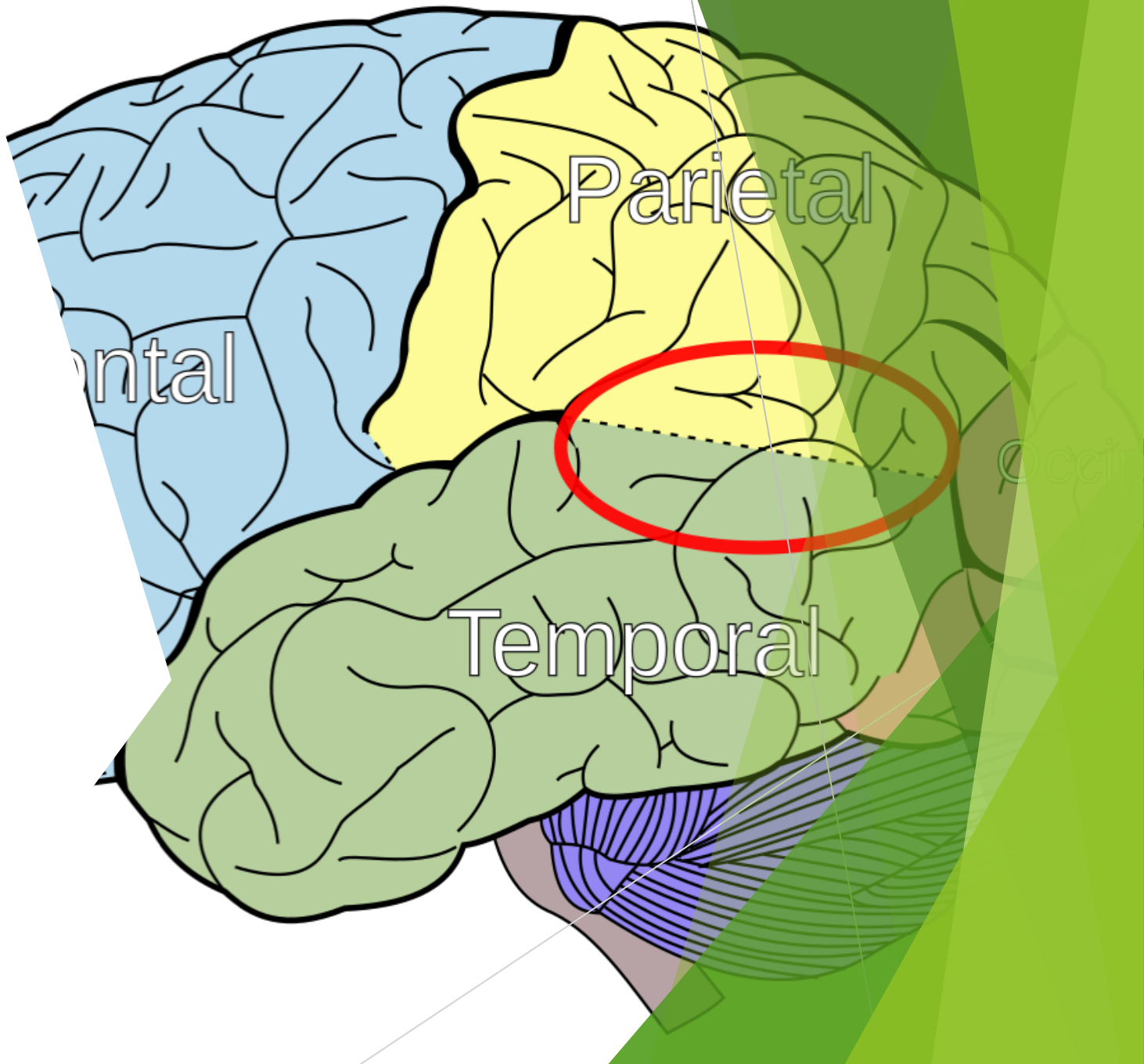
Tinnitus research

- Are findings related to tinnitus (state) or a predisposition for developing tinnitus (trait)?
- Compensatory mechanism in place? Result of auditory deprivation?
- Longitudinal studies to compare pre-post tinnitus
- Limited reliability of animal behavioral assessment in tinnitus
- Limited sensitivity for assessing auditory dysfunction in humans
- Not controlled for hearing loss

Neuromodulation

- Single session repetitive Transcranial Magnetic Stimulation
  - 11 studies, N=313 patients
  - Temporal or temporoparietal stimulation
  - Sham controlled studies
  - Transient effect on the tinnitus percept in 50% of the patients

- Repeated sessions of repetitive Transcranial Magnetic Stimulation
  - 21 studies, N=741 patients
  - 10 RCT's, n=234 patients
  - Temporal or temporoparietal stimulation
  - Low-frequency rTMS in trains of 1200-2000 pulses over 5-10 days
  - Overall significant reduction of tinnitus complaints (loudness, annoyance or both)
  - Which paradigm or stimulation target is unclear…



Neuronal correlates

- PET, SPECT, MEG, rsfMRI and EEG studies
- Limited amount of studies…
- Positive response related to the secondary auditory cortex bilateral
- Tinnitus reduction correlates with decrease of gamma and increase of alpha activity
- rTMS modulates thalamocortical activity

- Fundamental understanding of tinnitus

Transcranial Direct Current Stimulation

- Two studies, N=27 patients
- Left temporoparietal cortex stimulation
- Effect of anodal tDCS → increased cortical excitability
- More research is needed

Epidural Stimulation

- Modify neuronal activation in the auditory cortex
  - Based on a study in 43 patients and repeated in smaller samples
  - fMRI based targets
  - Burst stimulation more efficient than tonic stimulation
  - Decreased tinnitus loudness of 51%

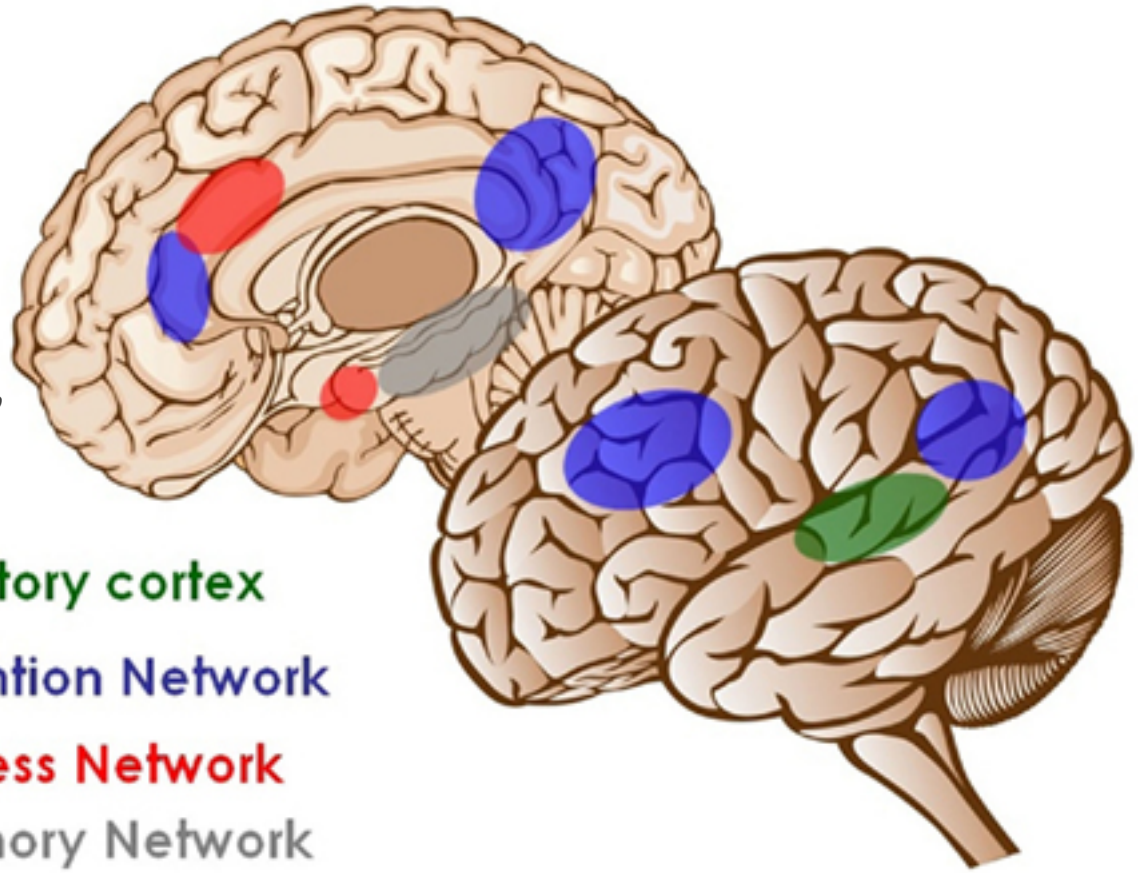
- Deep Brain Stimulation
  - Deeper brain structures
  - Network effect

Non-auditory brain areas

- Synchronously connected
- Awareness and salience brain networks
  - Inferior parietal cortex
  - Dorsolateral prefrontal cortex
  - Anterior cingulate cortex
  - Anterior insula
  - Posterior cingulate cortex
- Functional connection; auditory cortex → network of higher order areas
- Distress; anterior cingulate cortex, anterior insula and amygdala (pain network)
- Memory of phantom percept; hippocampus

Brain networks

1. Primary auditory cortex
2. Anterior/posterior cingulate, precuneus, parietal, frontal
3. Anterior cingulate
   Anterior insula
   Amygdala
4. Hippocampus, amygdala, parahippocampus

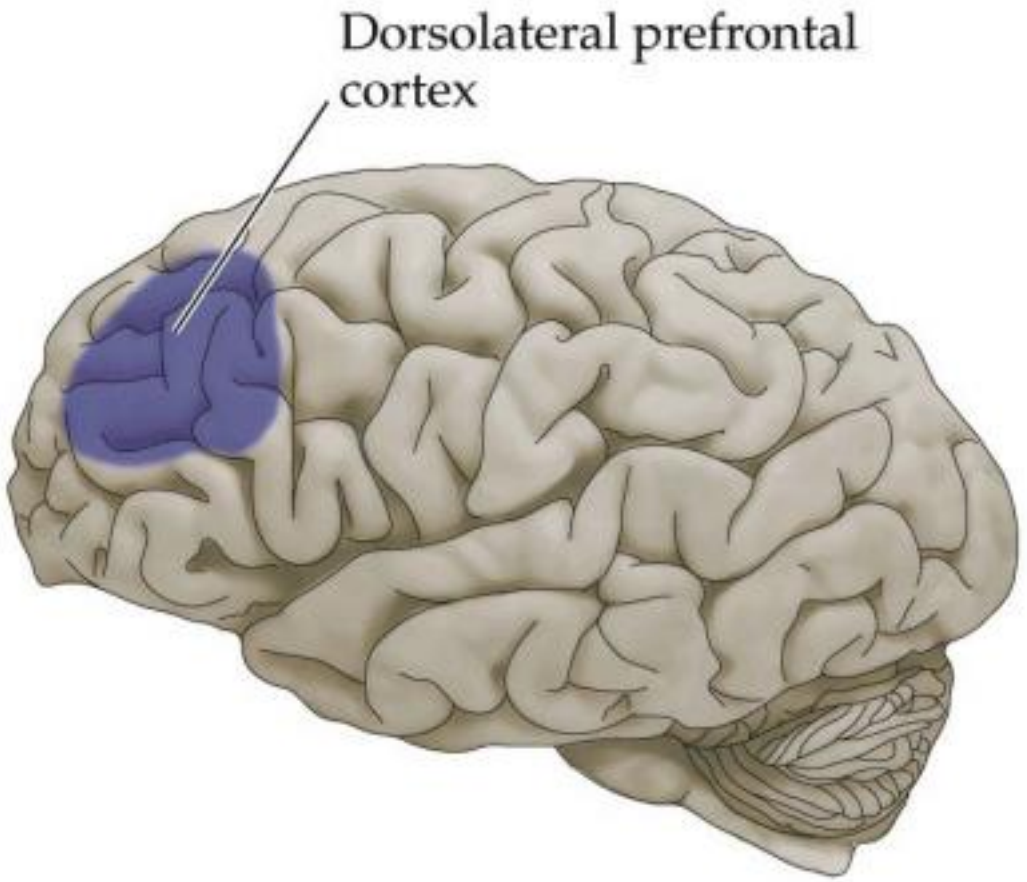


Modulation of non-auditory areas

- rTMS effects – single session
  - Based on studies by a co-author
  - Right dorsolateral prefrontal cortex
    - Auditory attention/processing/memory
  - Dorsal part of the anterior cingulate cortex
    - Reduced tinnitus intensity by 34% and distress by 26%
  - Ventrolateral prefrontal and Parietal cortex
    - One study by a co-author
    - Some effects were reported (reduced perception by 22%)
- Repeated sessions
  - Left dorsolateral prefrontal and temporal cortex combined
  - Tinnitus suppression after 3 months

Non-auditory brain areas (2)

- transcranial Direct Current Stimulation
- Target = dorsolateral prefrontal cortex
  - Tinnitus suppression in 30% of the participants
- Pathophysiological distinct forms of tinnitus
  - Interindividual variability
- Preliminary studies



Direct electric stimulation

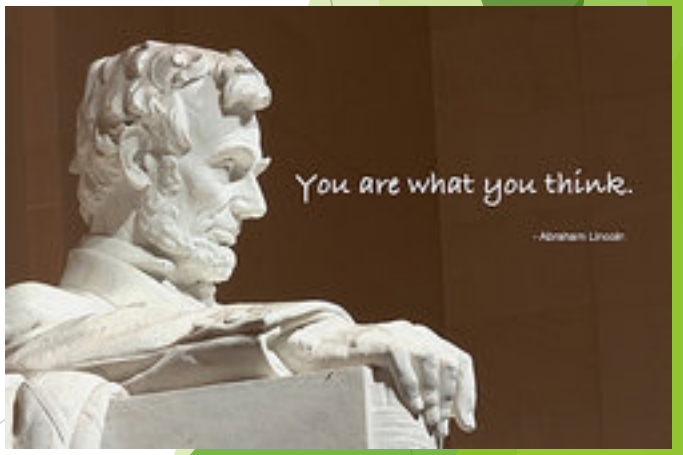
- Epidural electrodes
  - Dorsolateral prefrontal cortex (n=1)
  - Localization based on fMRI
  - Tinnitus reduced by 67%
- Deep Brain Stimulation
  - Very focal
  - No published reports for the treatment of tinnitus
  - Side effect of treatment for movement disorders
  - Stimulation of thalamus and caudate may provide relief

Limitations

- Distinct forms of tinnitus → pathophysiological difference
- More precision medicine, per individual required

- Reliable assessment of tinnitus symptoms
- Limited resolution and sensitivity of imaging techniques
- Sample sizes; fairly small

- Many reported studies were by the authors of the review paper
  - Self fulfilling prophecy



Conclusions

- Auditory cortex + a large network of brain regions showed structural and functional alterations in tinnitus
- Attention, distress and memory networks are involved
- Brain stimulation is complementary to neuroimaging
  - Aim for focal modulation of areas highlighted by functional imaging
- Changes in tinnitus reduction of worsening can reveal information about the neuronal changes
- Specific aspects of tinnitus need to be investigated
  - → distress, depression and loudness