Cortical activity associated with the detection of temporal gaps in tones

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Research Aim

Investigating spatiotemporal profiles to gaps in tones of within-frequency (WF) and between-frequency (BF). In this study, we focus on spatiotemporal profile of cortical responses.

Gap detection

(Phillips, et al., 1997)

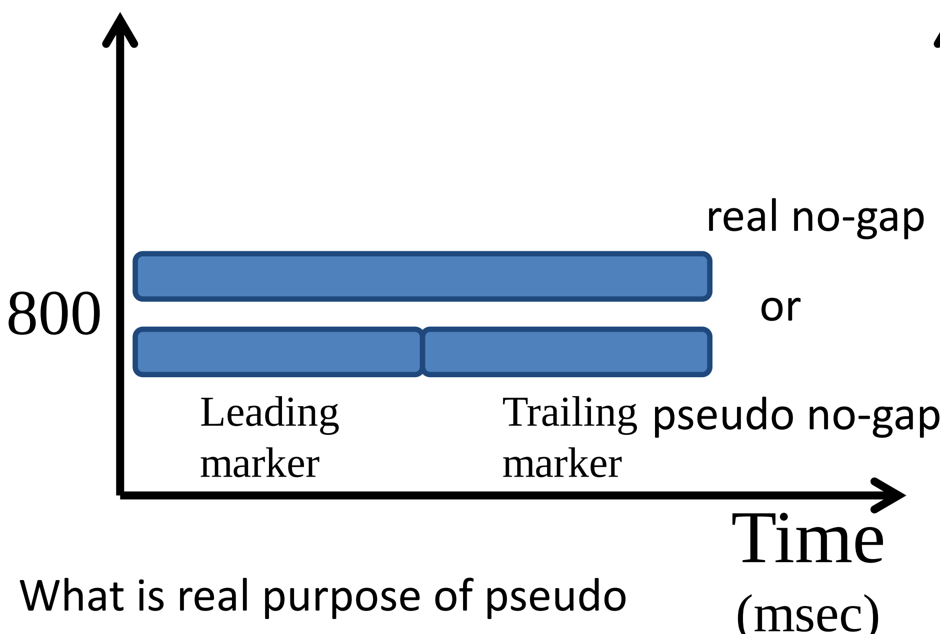
Within-frequency (WF) task

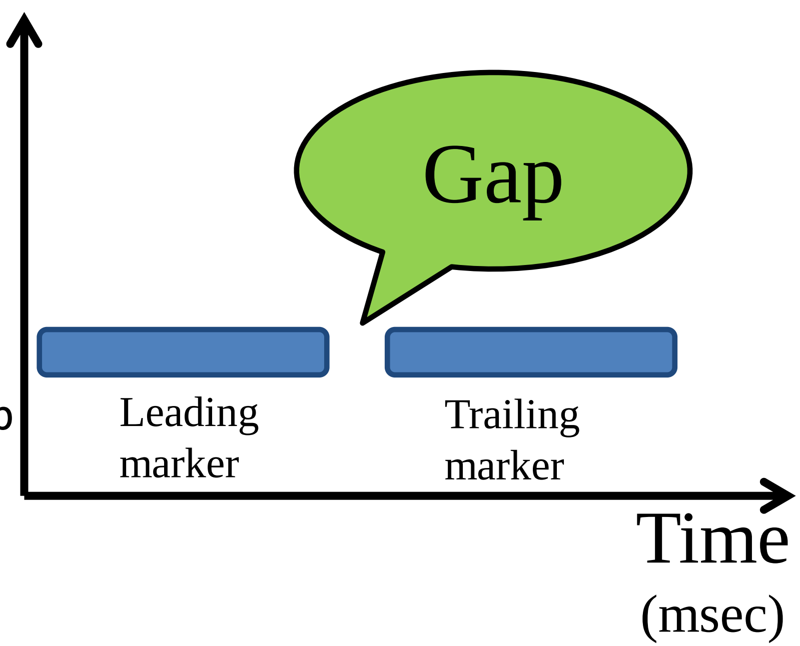
No gap

30-msec gap

In principle, two stimulus blocks are necessary to make silent period

Frequency (Hz)





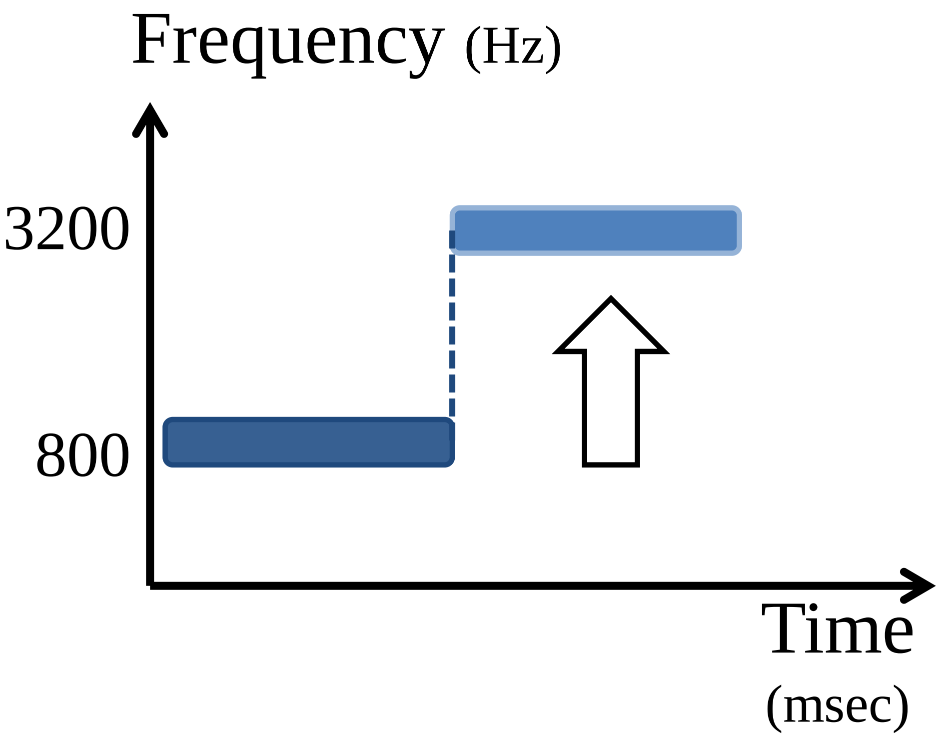
What is real purpose of pseudo no-gap?

Gap detection

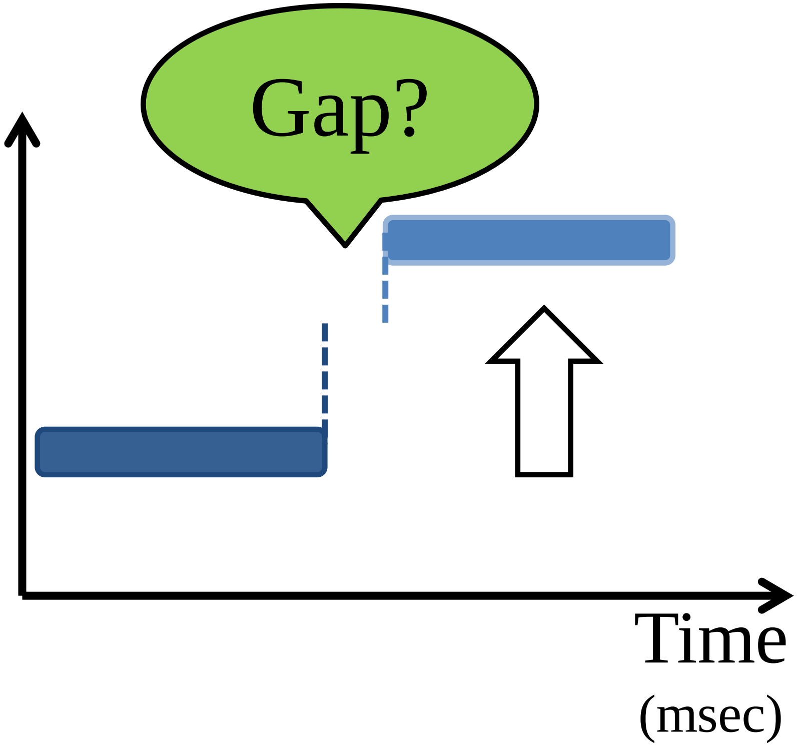
(Phillips, et al., 1997; Taylor et al., 1998)

Between-frequency (BF) task

No gap



30-msec gap



Why is gap detection so difficult when the frequency of the sounds before or after the gap is different?

To seek the answer…

Brain responses to gaps were measured by using magnetoenchephalogram (MEG).

This does not give complete answer, but should be informative as one step.

Experimental design

1) Two types of experiment were performed, the difference is the gap 0 ms settings.

Experiment 1, no onset for WF 0 ms, no rise/fall overlap for BF 0 ms.

Experiment 2, rise/fall overlap for BF 0 ms.

2) Used tone frequencies, 800Hz and 3200Hz.

3) Combination of frequency for gap detection

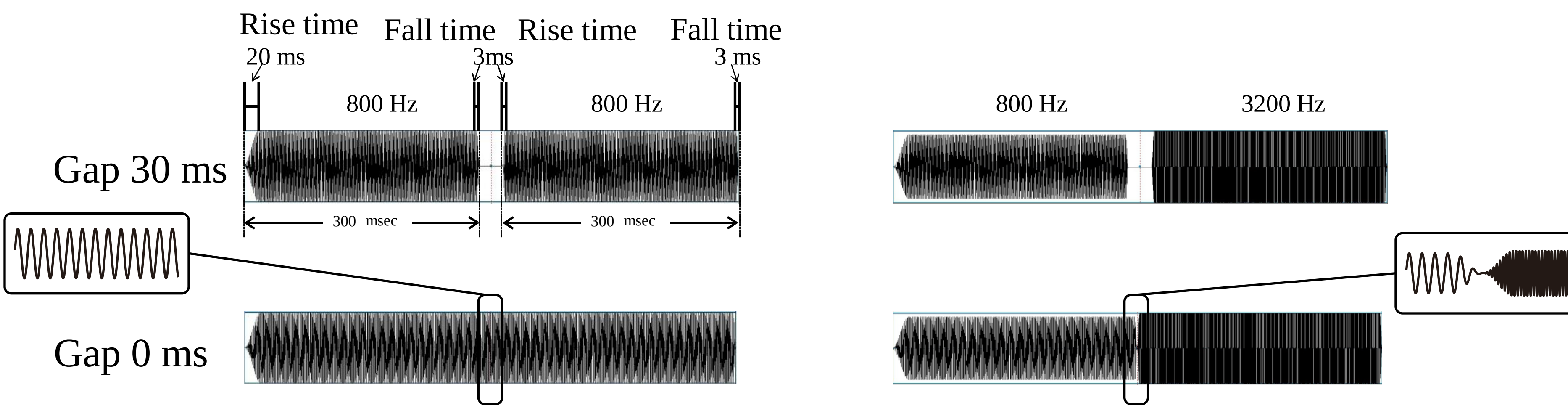
WF, 800Hz-800Hz, 3200Hz-3200Hz

BF, 800Hz-3200Hz, 3200Hz-800Hz

Design of Stimuli

Experiment 1

WF | BF



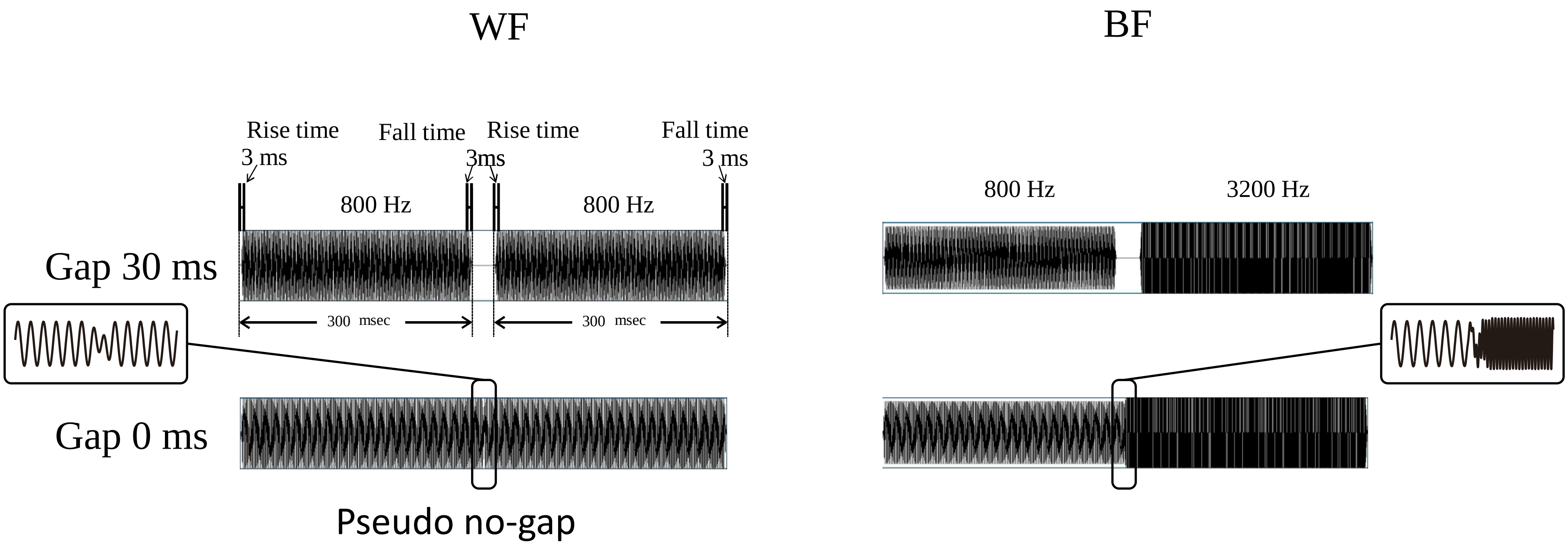
Continuous pure tone, which had no rise/fall times in the middle of the tone

Sequences of pure tones including rise/fall times with 0-ms gap

In WF gap 0 ms setting, continuous pure tone – no onset.
In BF gap 0 ms setting, the fall part of leading marker and the rise part of the trailing marker has no overlapped.

Design of Stimuli

Experiment 2



In gap 0 ms setting, the fall part of leading marker and the rise part of the trailing marker are overlapped

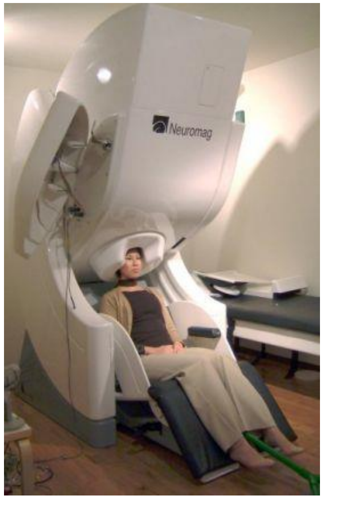
Magnetoencephalography recording

- Participants

  -- Experiment 1, Ten right handed healthy volunteers (five females and three males, aged 23-52 years)
  – Experiment 2, Six right handed healthy volunteers (four females, aged 23- 27 years)

- Magnetoencephalography recording

  – Recording: 306-channel Neuromag
  – Sampling rate 1000 Hz
  – On-line Digital Filtering 0.1-330 Hz
  – ISI: randomly varied from 1.5s to 1.8s
  – 80 trials for each combination

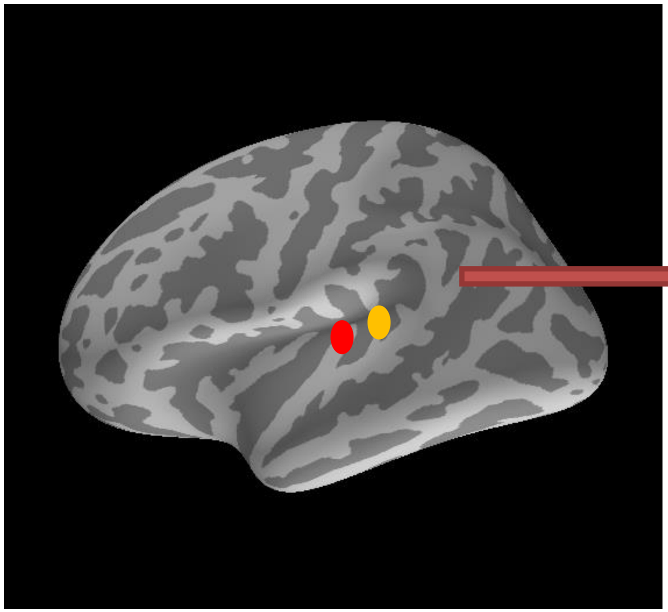


306-channel Neuromag Vectorview MEG (Elekta).

A Way of Analysis

Source Analysis

To determine ROI
ROI = region of interest

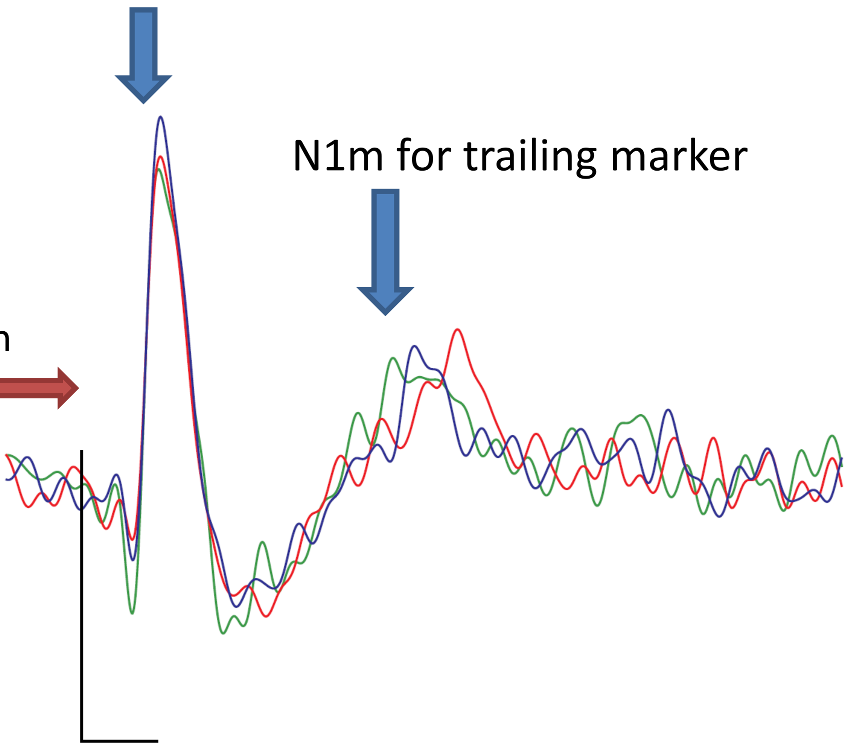


Regional
activation

Characteristics of time course brain activations

N1m for leading marker

N1m for trailing marker



Red-> 800Hz, Yellow -> 3200hz

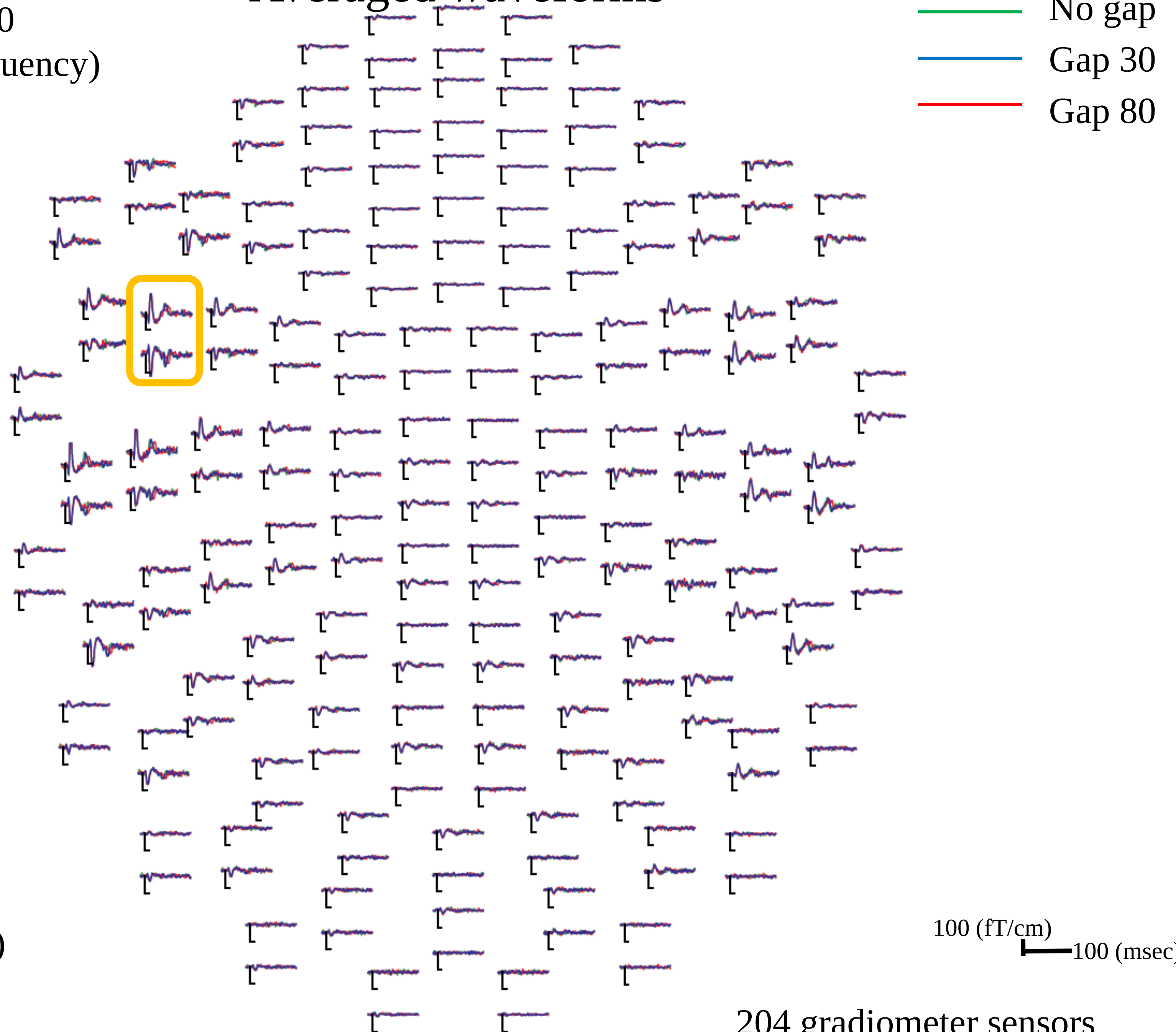
Tonotopic organization ?

We assume that response for trailing marker plays a important role for the gap detection mechanism, and focus on N1m response for trailing marker in this study.

Sensor level analysis
Experiment 1

Averaged waveforms

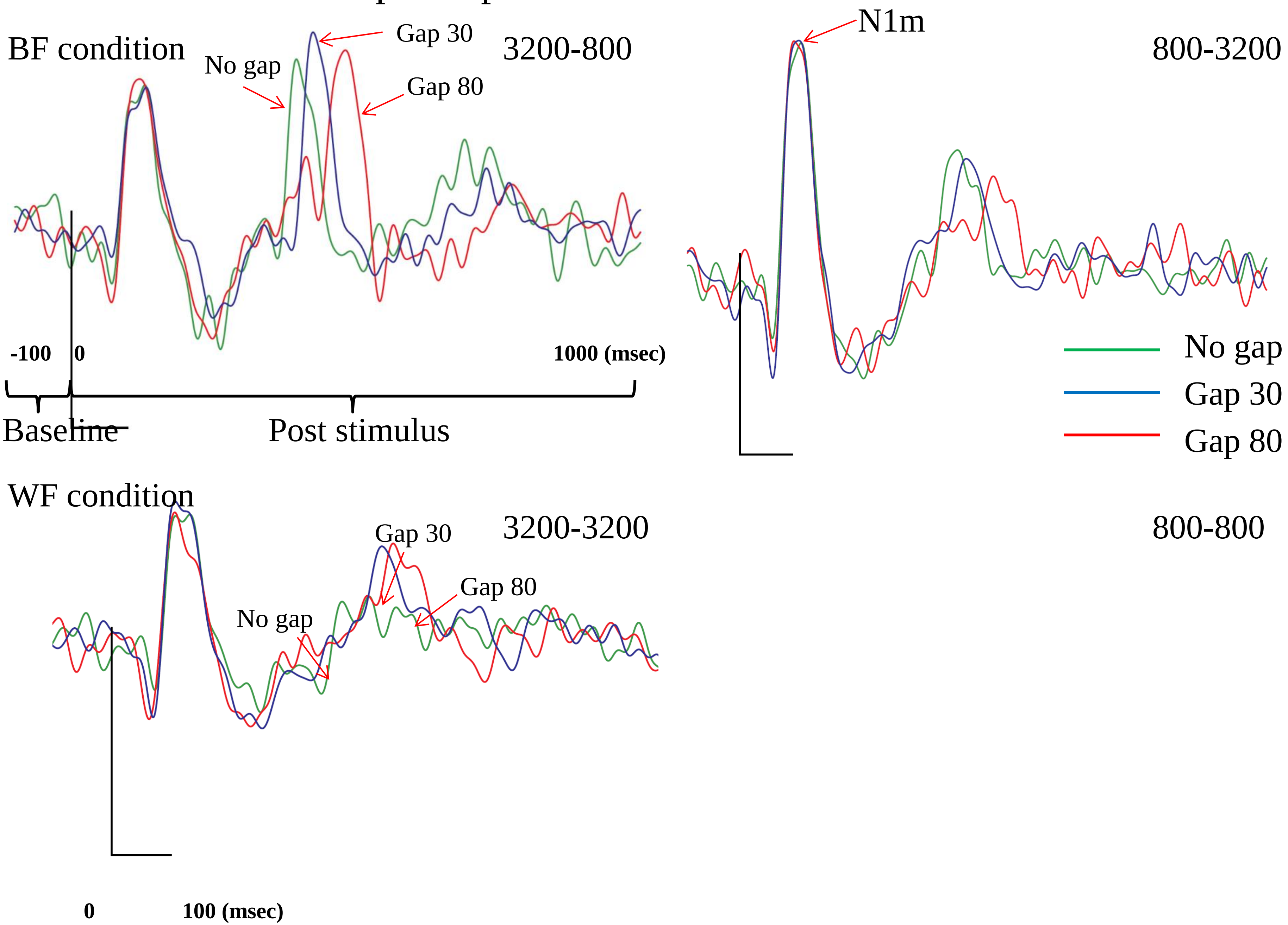
3200-800
(Between-frequency)



Right ear stimulation, and left hemisphere activations (contralateral)

204 gradiometer sensors

Experiment1, Representative activations of BF and WF conditions from one participant and one sensitive sensor



MEG source analysis

Procedure

1. Pick up N1m latencies from sensor and RA in primary auditory cortex ROI.
2. Extract the source activation map at selected latencies.
3. Transforming above activation maps into standard brain and average these with standardization.

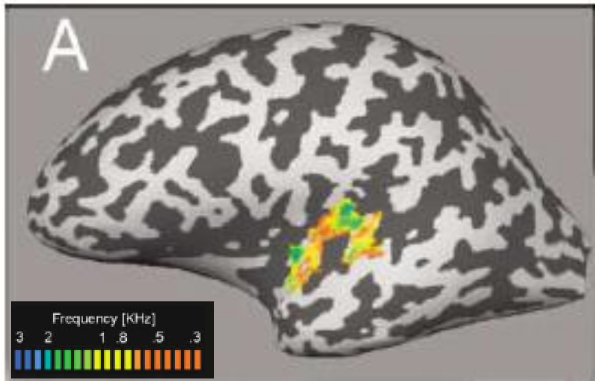
→ Slide 17

4. Marking the individual ROI for 3200hz and 800Hz with referencing to above ROI obtained in procedure 3 and general fMRI results.

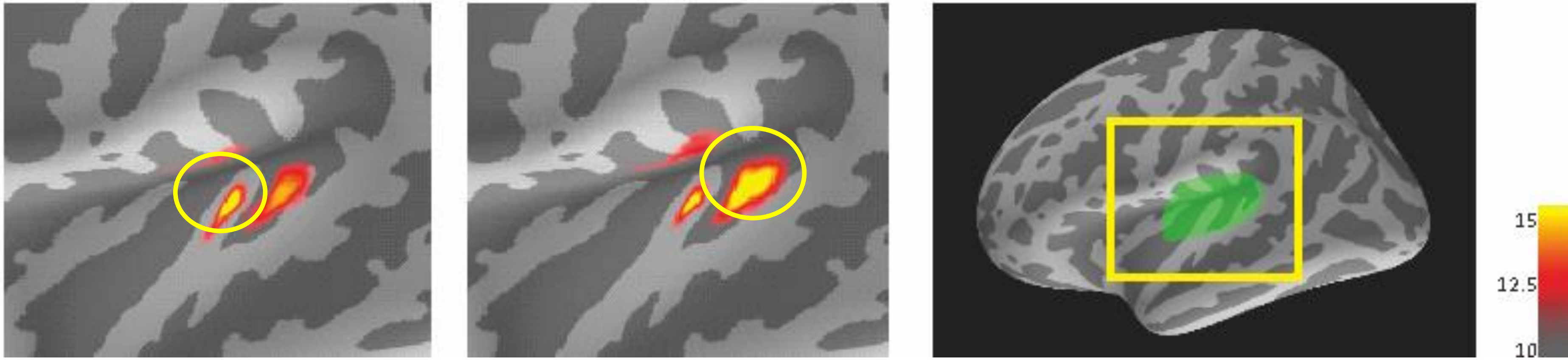
→ Slide 18, 19. (Slide 20 shows the averaged results of activations on inspection ROIs)

5. Extract the regional activations (source waveform) and analyze the N1m responses to trailing marker.

Superimpose all ten participants' brain activities onto the standard brain.



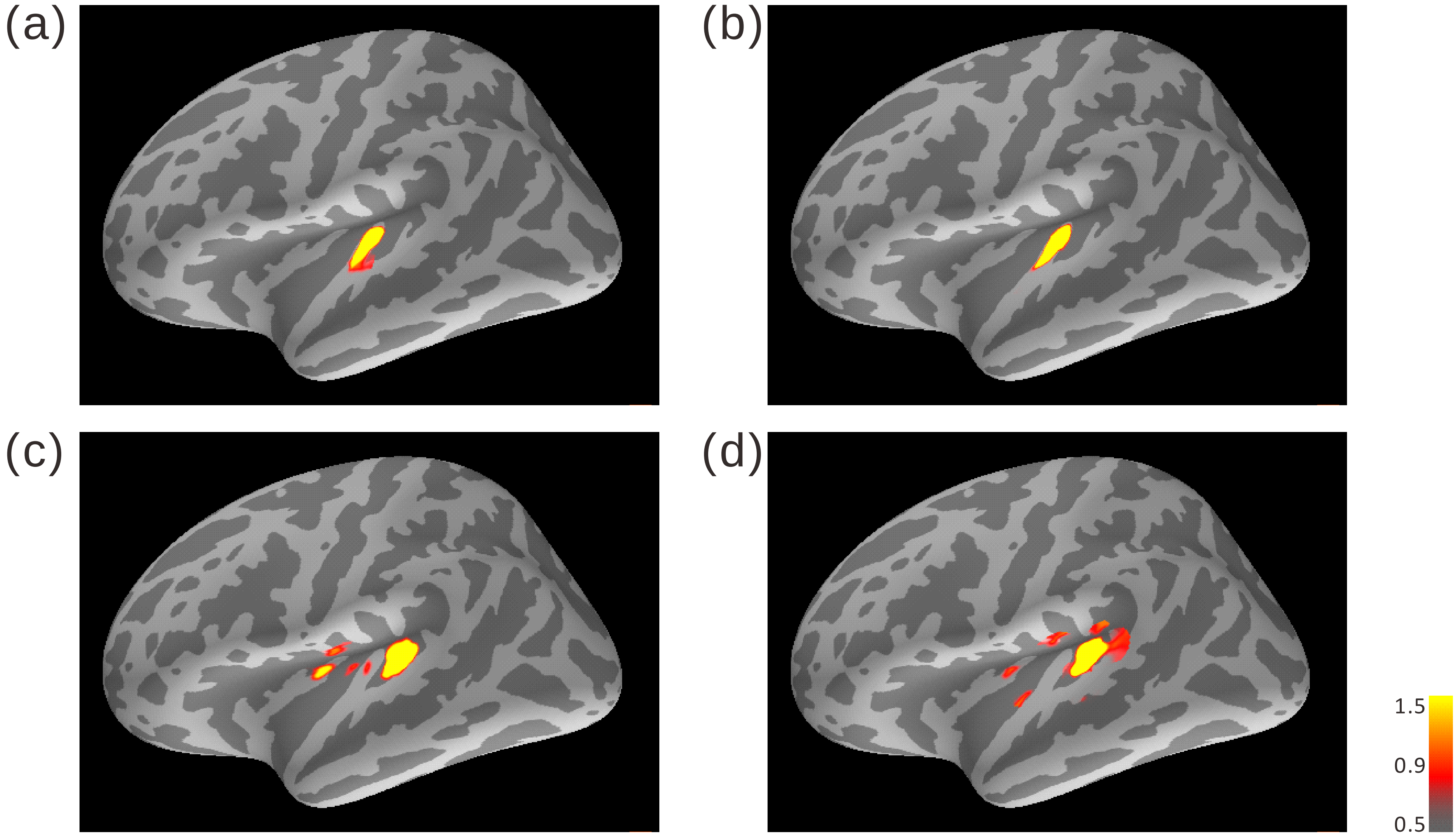
(Formisano, et al., 2003, Fig. 3(A))



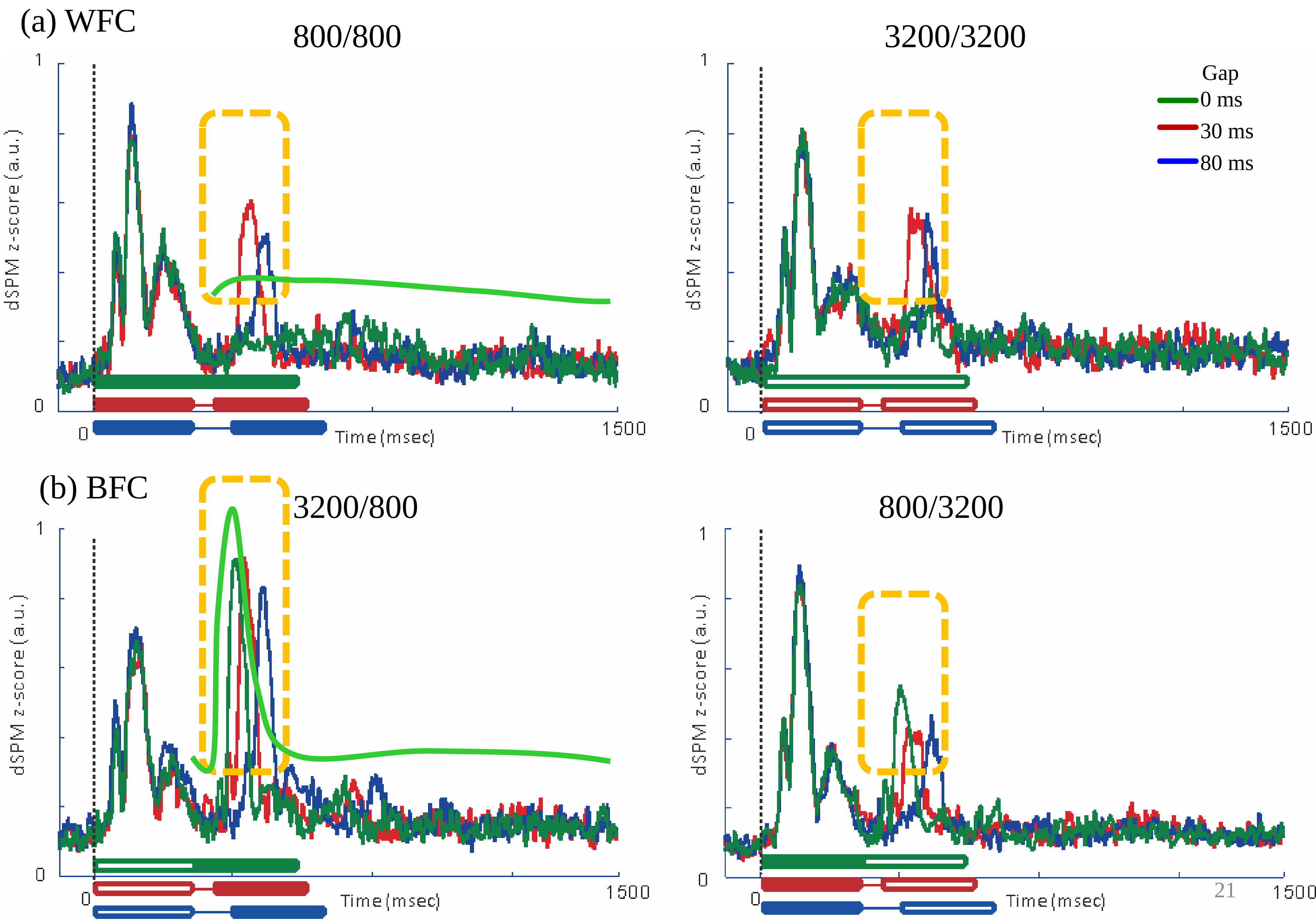
800Hz 3200Hz

Activation for 800Hz stimulus located at anterior side of Heschl's gyrus.
Activations shift to posterior side when using 3200Hz stimulus.

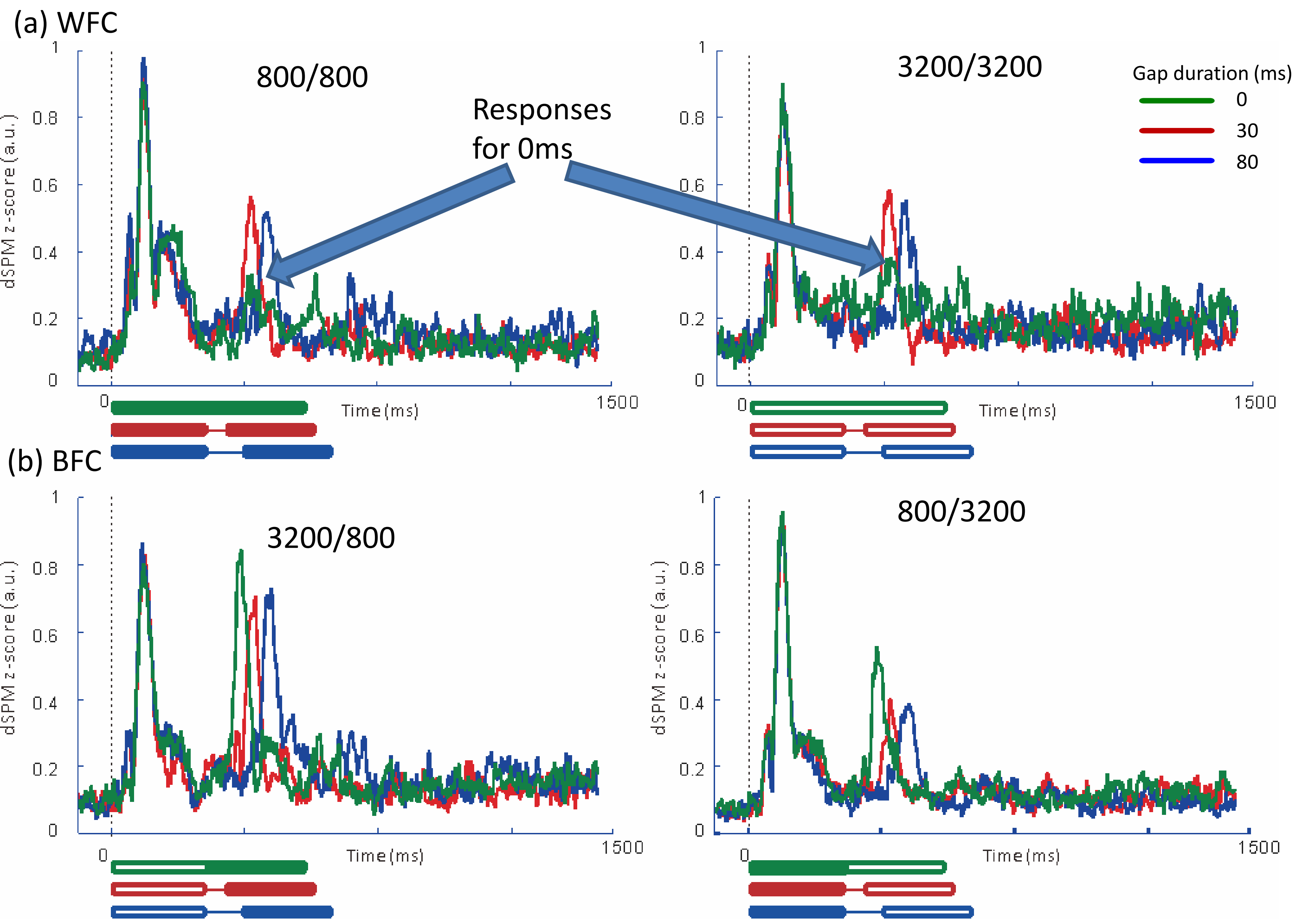
Mean activations in response to the trailing marker depicted on the standard brain for each condition



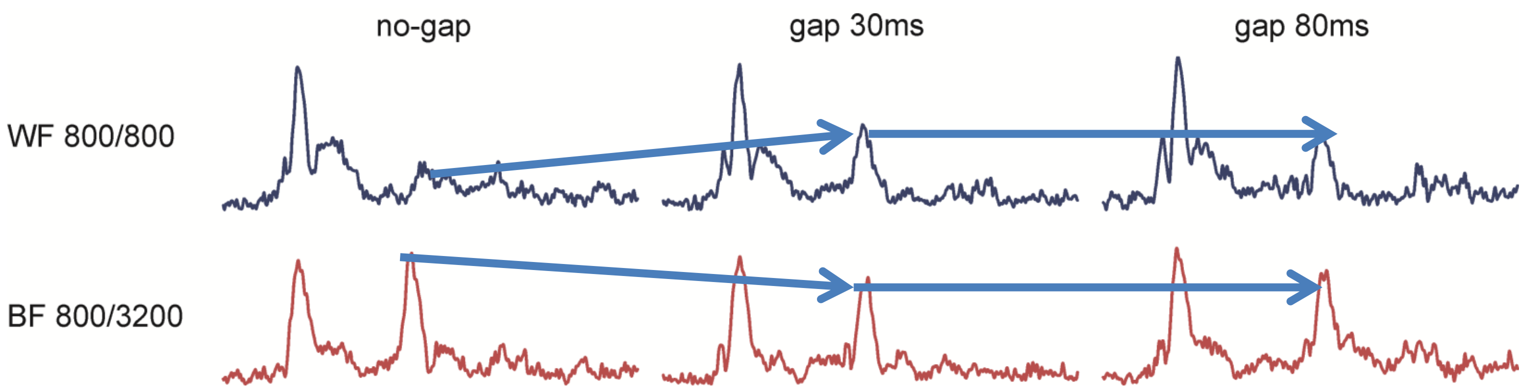
Experiment1, Mean regional activations in marked inspection ROIs for all six participants.



Experiment2, Mean regional activations in marked inspection ROIs for all ten participants.



Relation between gap setting length and N1m amplitude strength



In WF, it starts from smaller N1m responses at gap-0 (experiment 2), starting with increasing.

In BF, it starts from larger N1m responses at gap-0. starting with decreasing.

noite: In this figure, amplitude is z-score and standardized.

Summary of the results

1. Brain Activation area
   - 800 Hz：anterior side of Heschl's gyrus
   - 3200 Hz：posterior side of Heschl's gyrus
2. Regional Activations
   - 0ms Gap in WFC (continuous tone)： No onset
   - Small dip (3.0 ms) in WFC: small onset responses and depends on each individual.
   - 0ms Gap in BFC：always have clear onset responses.
3. Within Frequency and Between Frequency

   WF：Stable activation pattern in space and time

   BF：Varies due to stimulation pattern in time and dispersion in space

Previous studies

Understanding of temporal characteristic by M/EEG sensor analysis

EEG studies;
MMN (Heinrich, et al., 2004)
N1-P1-N2 (Lister, et al., 2007)

MEG studies;
Witton, et al. (2012) NeuroImage. 63(3), 1249–1256.
Bernhard, et al. (2010) PLoS ONE. 5(4): e10101.

Discussion

M/EEG sensor detection is always a mixture of several components from multiple areas.

MEG source analysis makes it available to focus on restricted cortical area.

In gap detection study, tonotopical organization has NOT been taking account.

No study has examined the gap detection processing with 'BF' task. Also no study has performed source analysis.

Brief Conclusion

We showed frequency sensitive brain activities based on tonotopic organization in the human primary auditory cortex related to Gap detection.

The activation pattern and RA are clear and robust spatially and temporally when using WF stimuli, while they are more ambiguous when using BF stimuli.

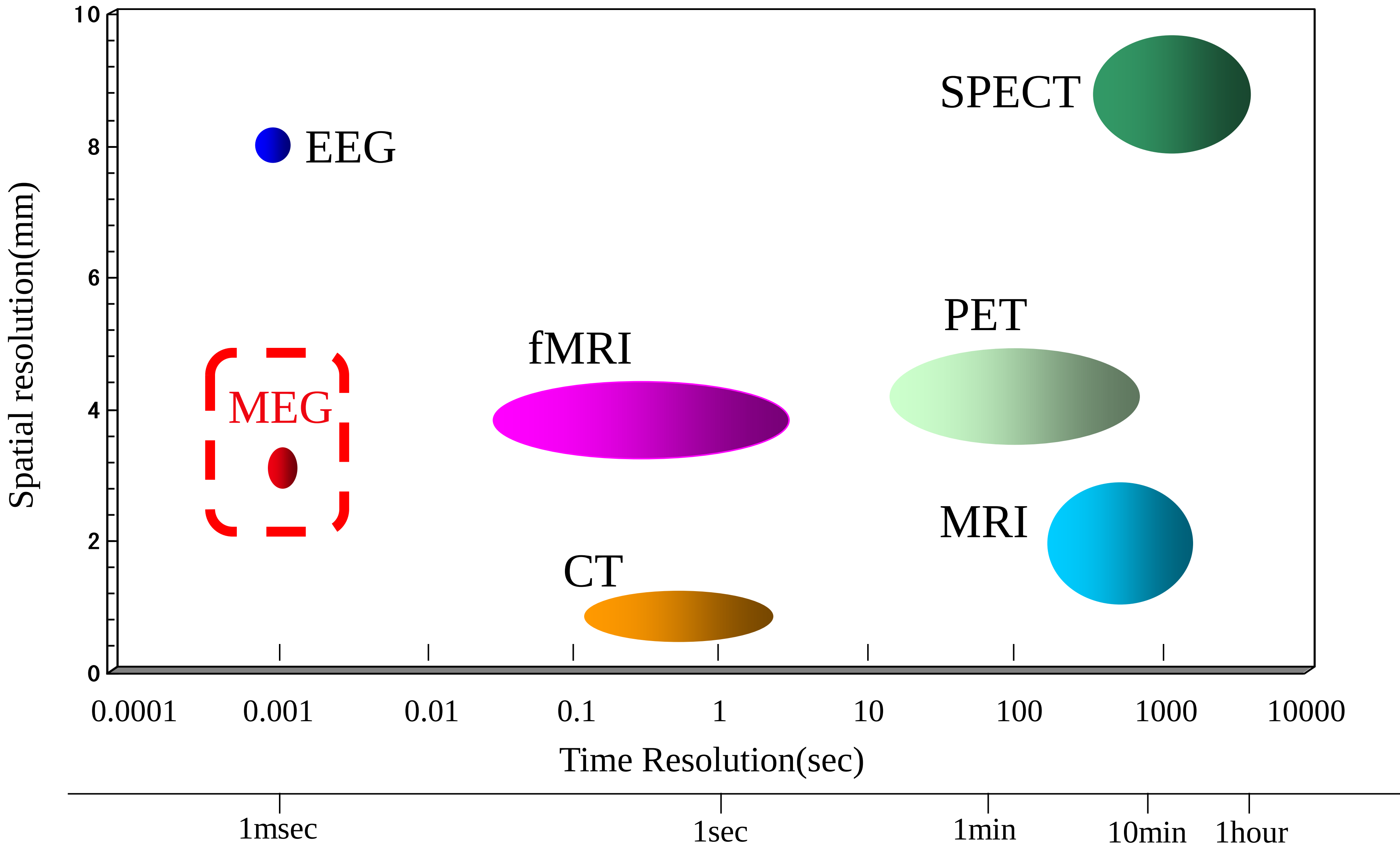
In WF, less activities when using small gap (pseudo no-gap) . In BF, higher activities even using no Gap condition.

What is required?

Absolutely, the integrated studies of behavioral experiment and brain measurement are necessary.

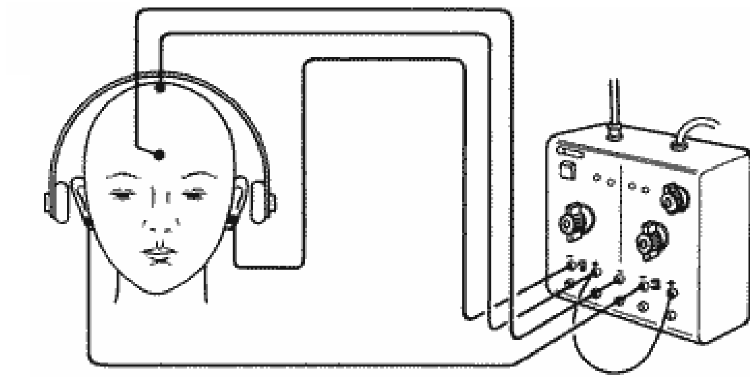
Our Direction

Combination studies of
ABR <-> ERP <-> MEG <-> fMRI <-> Behavioral experiment



Spatial resolution(mm)
10
8
6
4
2
0
EEG
SPECT
PET
fMRI
MEG
MRI
CT
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
Time Resolution(sec)
1msec
1sec
1min
10min
1hour

Schematic image of multiple modalities

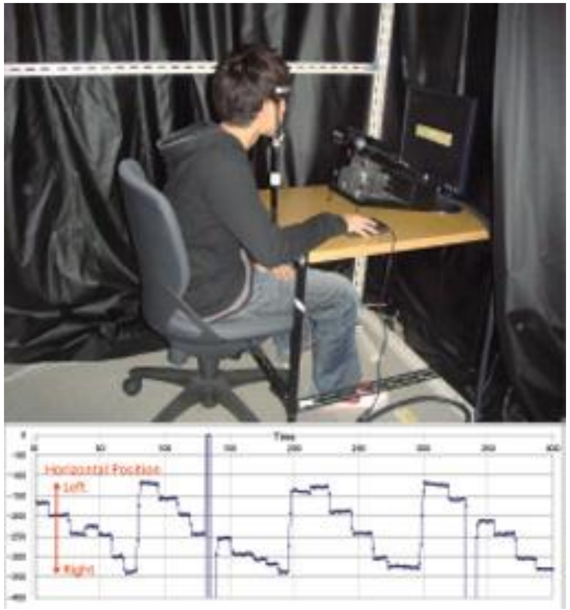


ABR

EEG

MEG

fMRI



Behavioral experiment

How to utilize multiple modalities for gap detection

ABR ⟺ (ERP, MEG) (signal analysis in time and frequency domain)

This integration makes possible to figure out the relation between cranial nerve Ⅷ and auditory cortex. How input signal is processed in auditory periphery (ABR) and what kind of information will be passed to cortex.

MEG ⟺ fMRI (analysis of spatial brain activities in time)

This combination is one of the most popular approach in current neuroimaging technique. fMRI provides trustable and stable spatial resolution and MEG keeps higher temporal resolution. In gap detection studies, we will examine which parts of the brain is responsible for detecting gap information.

(MEG, fMRI) ⟺ behavioral experiment (relation between higher order brain function and behavioral analysis)

The final decision whether or not there was a small gap during task was achieved somewhere in the frontal brain area, we believe. The brain response to the trailing marker and behavioral judgment should be involved in gap detection.

Joint collaboration

ABR, ERP Department of informatics, Faculty of information science, Kyusyu-University
Drs. Mori, Mitsudo and Ms. Kondo

MEG, Brain Center, Kyushu University
Hironaga,

fMRI, Kouch Institute of Technology
Dr. Kimura

My Role

Improvement of MEG measurement and analysis

MEG fundamental three factors for source analysis

(1) Forward/Inverse algorithm
the algorithm of the forward and inverse problems used to identify the source of the signal.

(2) S/N ratio
Preprocessing of the MEG signal

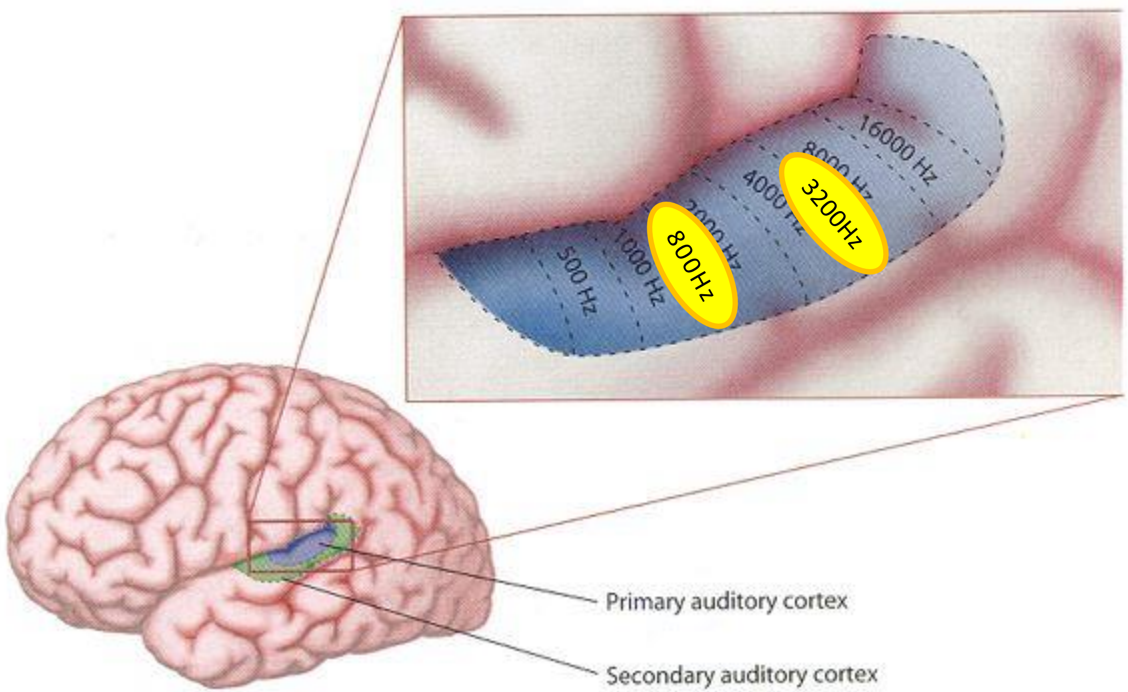
(3) MEG-MRI co-registration
precise alignment of the brain position to the anatomical image obtained by magnetic resonance imaging (MRI).

Tonotopy
Preliminary for the source analysis

Tonotopic organization

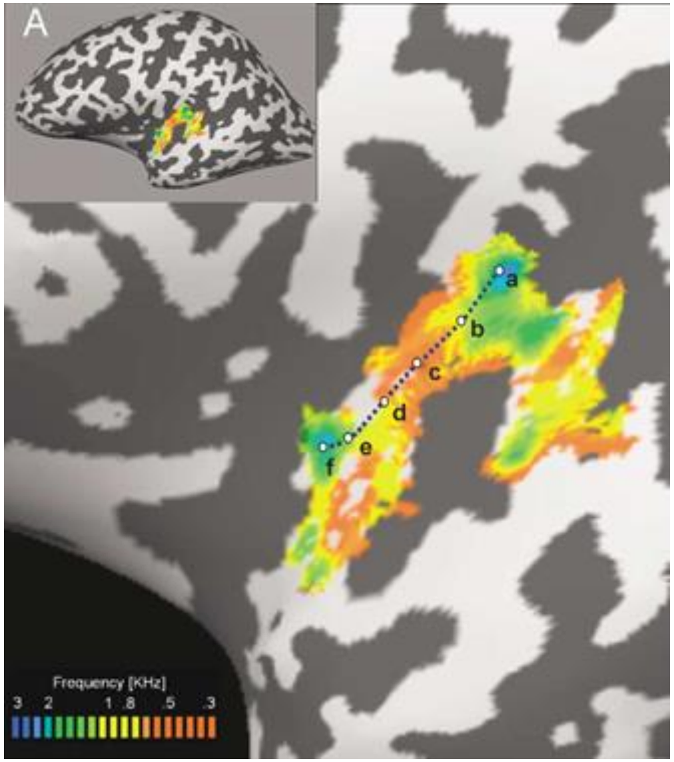
Cortical tonotopy

In human auditory cortex, frequency is encoded as place information.

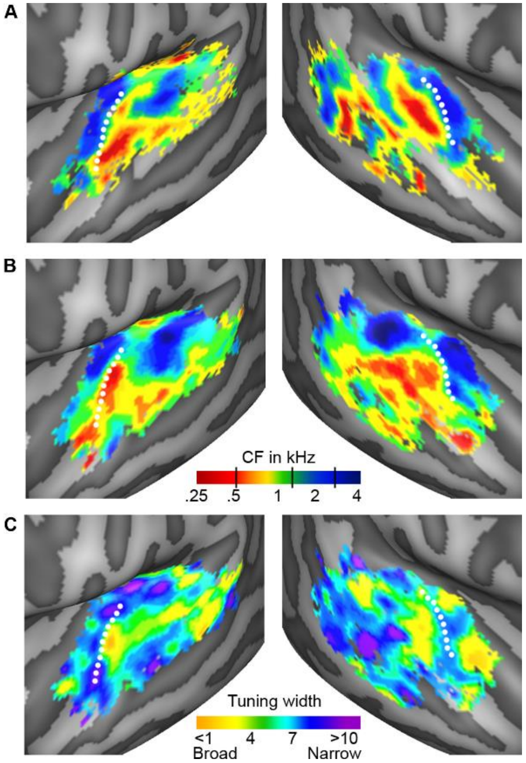


Practically, tonotopy is not simply aligned like somatotopy.

Recent fMRI study



(Formisano et al., 2003)



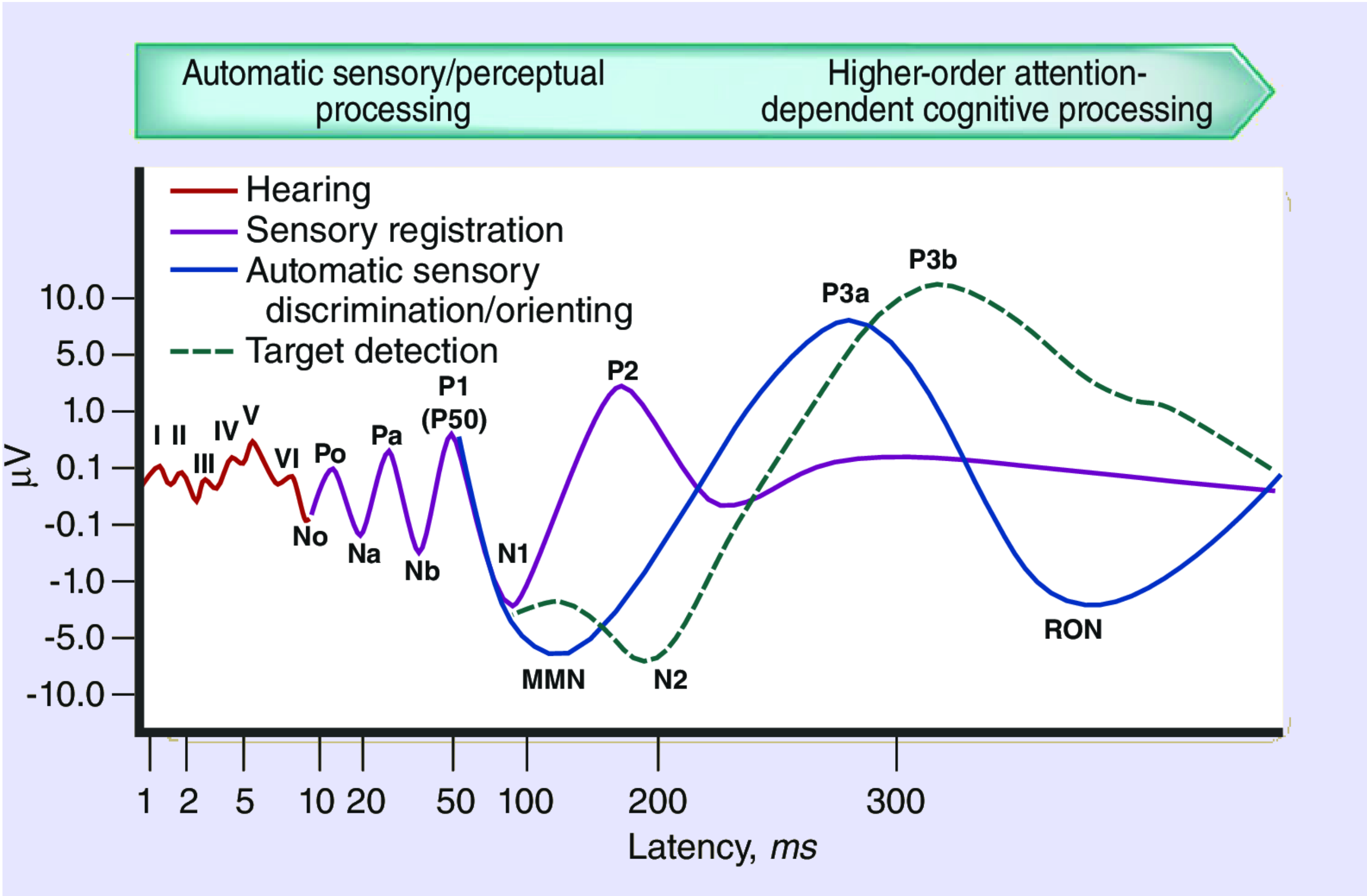
(Moerel et al., 2012)

Even using fMRI, it is not simply aligned and further it varies from individula to individual.

fMRI has higher special resolution, but lower time resolution.
Impossible to investigate exact timing for brain activation.

Relation between auditory response and onset time, EEG/MEG

(Picton et al., 1974)



In principle;

N_0 9ms

P_0 12ms

N_a 16ms

P_a 25ms

N_b 36ms

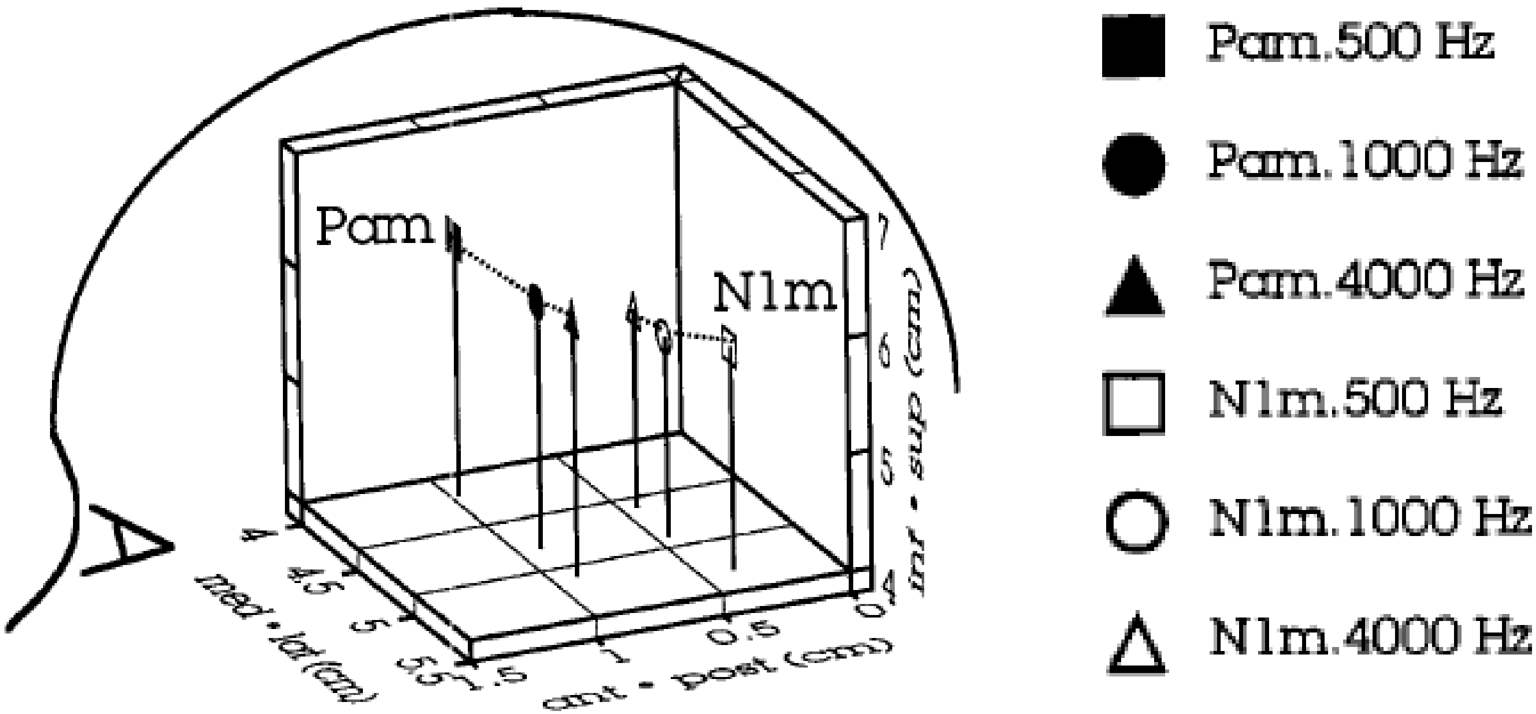
P_1 50ms

N_1 100ms

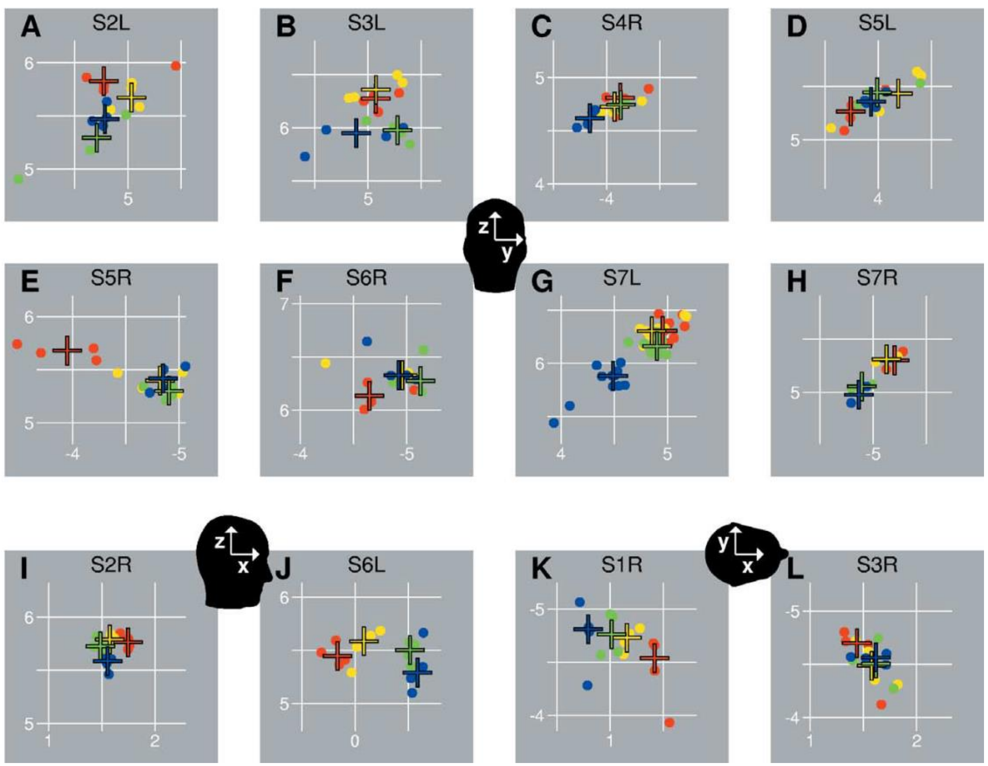
Many researchers interest in when and where brain areas are activated by what

One report for mirror symmetry and latency
(C. Pantev et al., 1995)

In Pam(30ms), responses shift to shallower position in Sylvian fissure according to frequency increase.
In N1m(100ms), responses shift to deeper position in Sylvian fissure according to frequency increase.
Above two responses likely keep mirror symmetry position



N1m frequency dependence
(Lutkenhoner et al., 2003)



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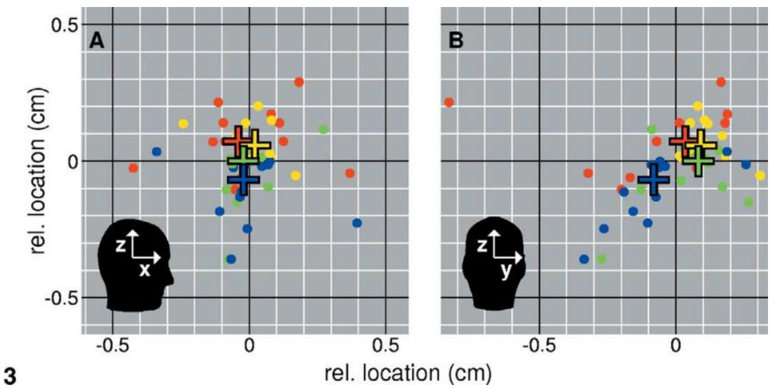


3

red 250Hz, yellow 500Hz, green 100Hz, blue 2000Hz

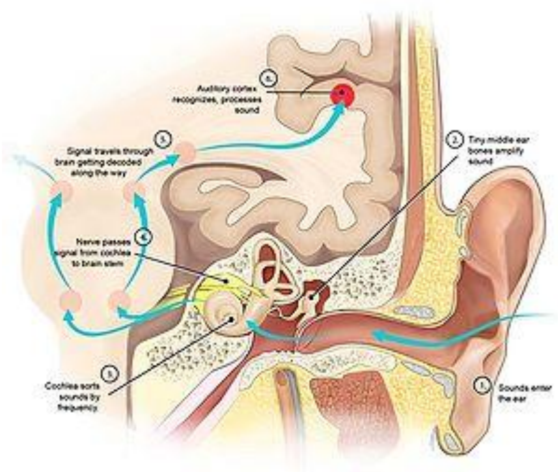
Left : Individual results

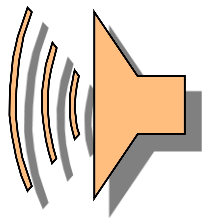
Upper : overplot

Authors claimed less frequency dependence in N1m response. At least, it seems like infeasible using dipole approach they said.

Other approach (e.g. distributed analysis) should be examined.

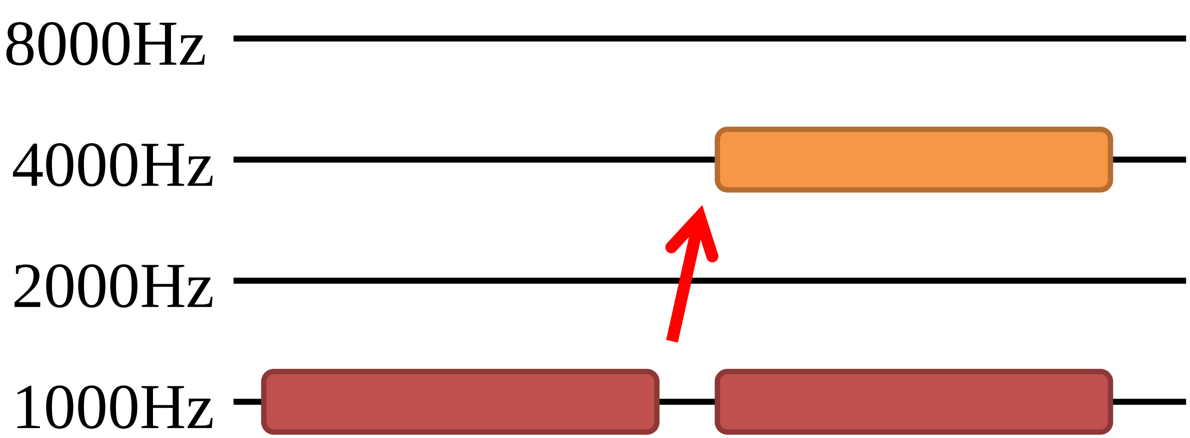
Across-channel processing
(What is this?)





Within-frequency (WF) condition
→ Discontinuity detection

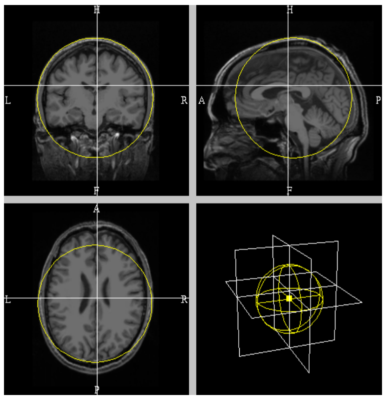
Between-frequency (BF) condition
→ Relative timing operation



How does this relate to tonotopy orgnization?

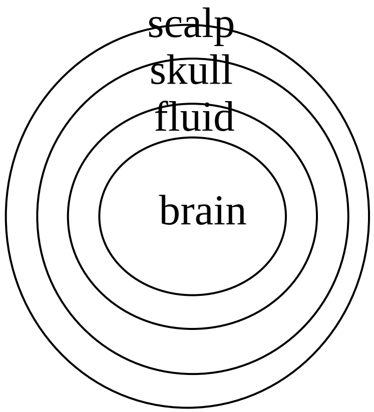
forward solution

Forward solution is the calculation formula from source information to sensor detection. In M/EEG, it depends on head modeling.



Spherical model

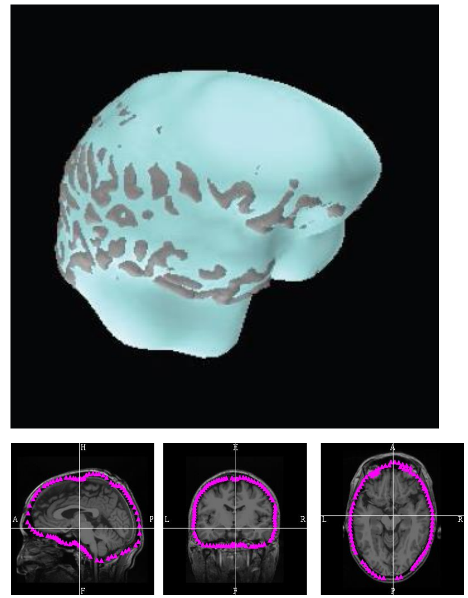
Basic approach in MEG、Sarvas formula(1987).



Multi sphere

Classical basic approach in EEG ～1950’s.

A problem; No one knows exact conduc- tivity in living human.



Homogenous model

Mainly employed in MEG.

Culurus of variation (BEM,FEM)

Piece-wise Homogenous model

Exact model for EEGで inverse solution.

Culurus of variation (BEM,FEM)

Inverse solution

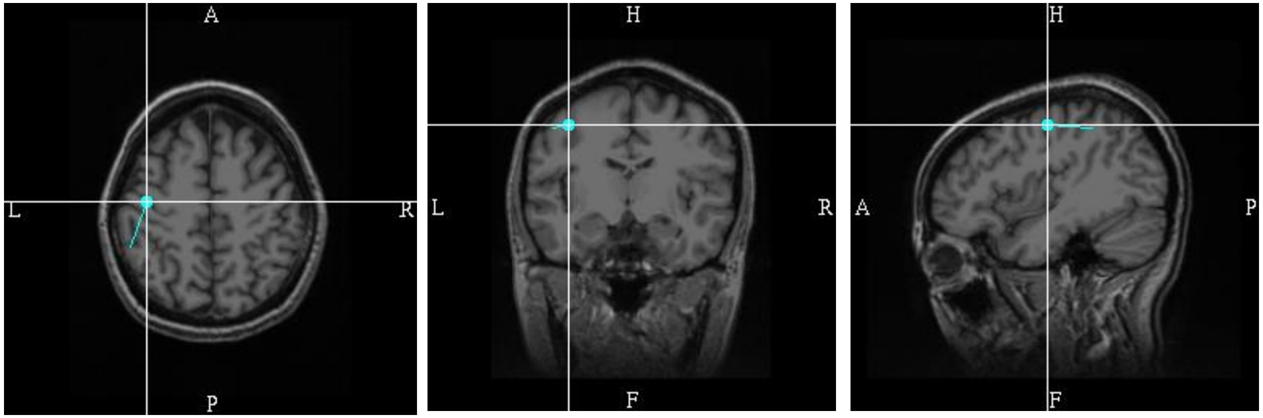
Equivalent Current Dipole

・Overdetermined solution (Number of variables < Number of equations)
Due to above, no solution exists. Therefore, it search the solution which minimize the error between modeled solution and measured values.

・Since location is not fixed, this approach is non-linear and iterative function minimization is performed.

・Initial position is one of important issue to avoid local minimum problem.

Advanced approach:
Moving dipole, spatio-temporal, Multi dipole, (RAP)MUSIC, Genetic algorithm

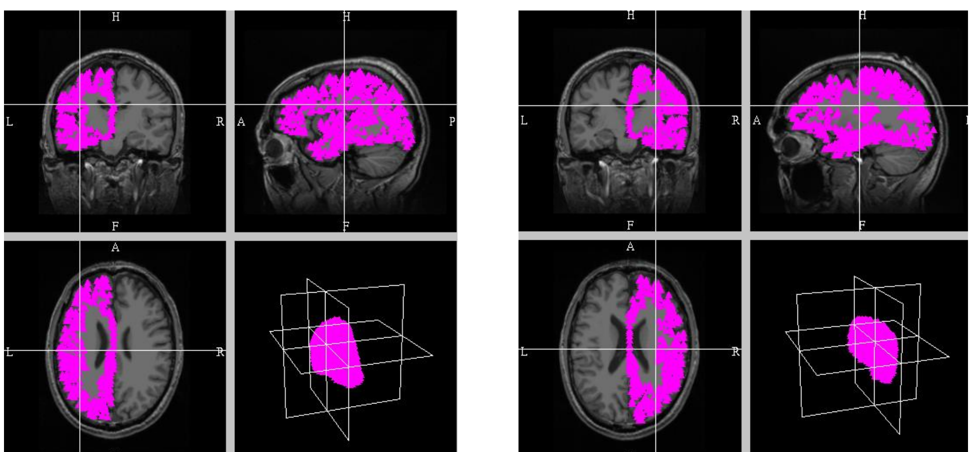


Distributed source analysis

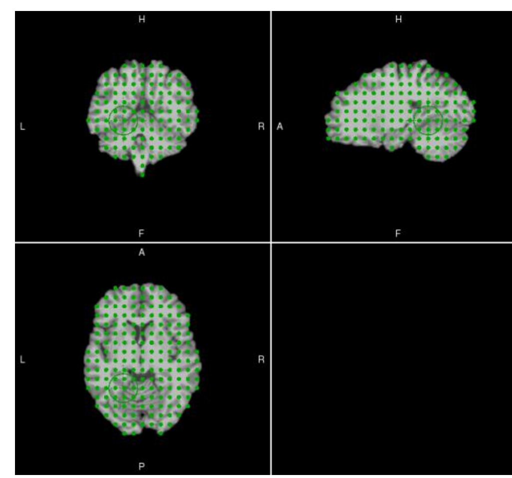
exhaustive search (dipole method) or
grid fixation in advance.
By fixating the grid, it can be treated as linear approach.

Dipole method —> non-linear、iterative function minimization
MNE, sLORETTA —> linear, pseudo-inverse, reguralization

Source grid points



MNE, Gray/White matter



BeamFormer, whole brain

Minimum Norm Method （concept）

Since this approach is linear, it can be expressed;

$$M=Lq$$

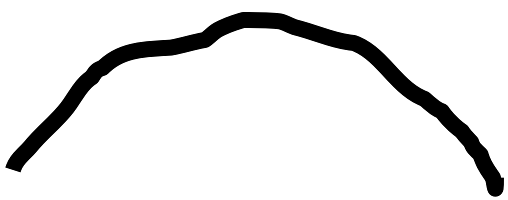
M, MEG observation, *L* lead field (forward solution), *q* unit dipole on each grid,

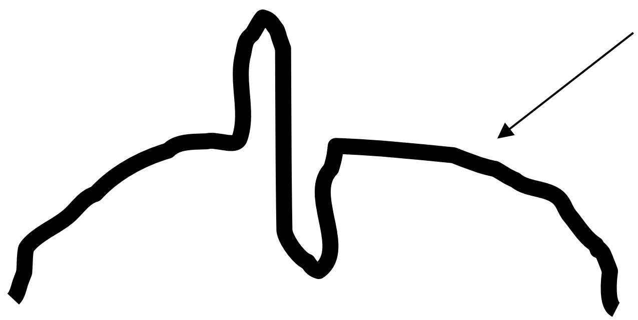
Due to underdetermined solution (Number of variables < Number of equations), there exists an infinite number of solutions.

We have to find an optimized solution among an infinite number of solution, by restricting the condition.

⇒ Minimizing the norm

Normal distribution-> norm is relatively small





Norm become larger if solution is like this.

Assume distribution of potential

Minimum Norm Estimates (MNE) (e.g. Molins et al., 2008)

$$M=Lq+n$$

M: MEG observation, L: Lead Field Matrix, q: source activation, n:noise

$$x' = \min_{q}\{\|Lq - M\|_C^2 + \|q\|_R^2\}$$
$$\|Lq - M\|_C^2 = (Lq - M)^T C^{-1}(Lq - M)$$
$$\|q\|_R^2 = q^T R^{-1}(q)$$

C: Sensor covariance matrix (e.g. pre-trigger period)
R:Source covariance matrix (e.g. fMRI results)

This formula minimize the sum of two norms, error (differential between modeled calculation and detection) and potential distribution

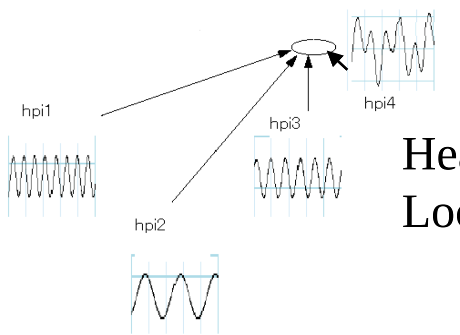
Using Lagrange multiplier and regularization parameter (λ^2) *, general solution is given by;*

$$W = RL^T(LRL^T + \lambda^2 C)$$

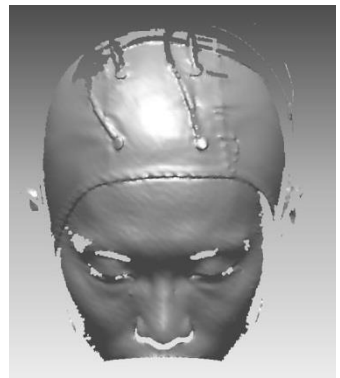
Improvement of MEG-MRI co-registration

3D laser scanning technique

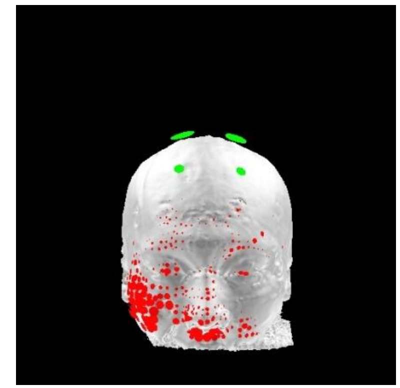
Co-registration 2, Procedure



Head Localization



Fiducial points (LPA, NA, RPA)



device coordinate

Head flame

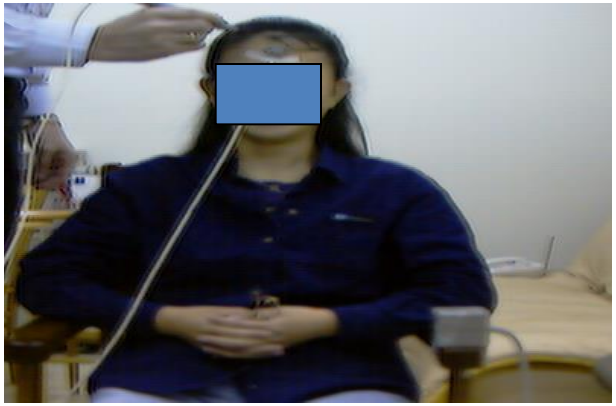
RAS coordinate

3. Hpi coil is a solenoid, and it behaves as magnetic field generator. Before MEG measurement, we can obtain the position of HPIs in device coordinate.

1. Put four HPI coils on the cap during MEG measurement. Using 3D digitizer head and face shape and position of HPIs and fiducial points are obtained

2. By registering the 3D digitization results with MRI contour, we can obtain the positions of HPIs and fiducial points on the MRI coordinate.

Co-registration 3, Polhemus System



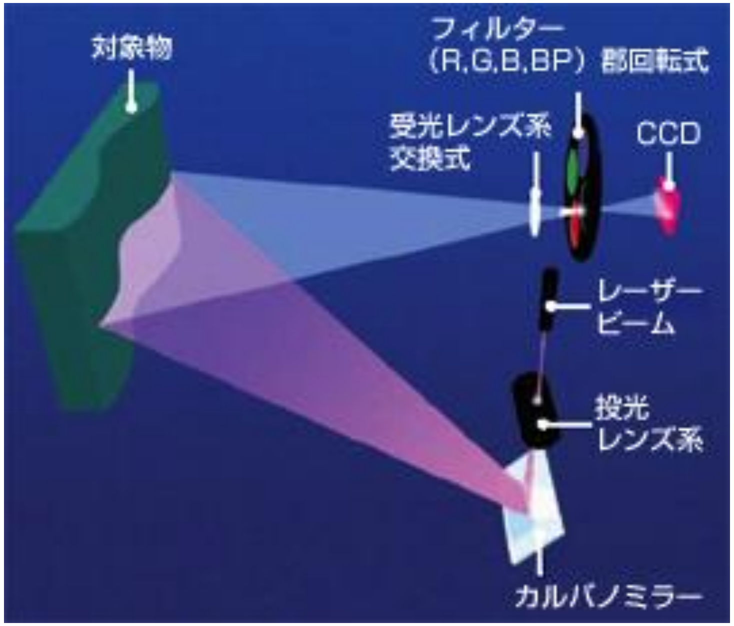
In generally, above polhemus 3D digitizer (magnetic field digitizer) has been widely used in MEG users.

One problem with this technique is the sharpen pen type sensor,

・This technique suits for the measuring of rigid objects, but problematic for human face. Especially for infants and phychartric patients.

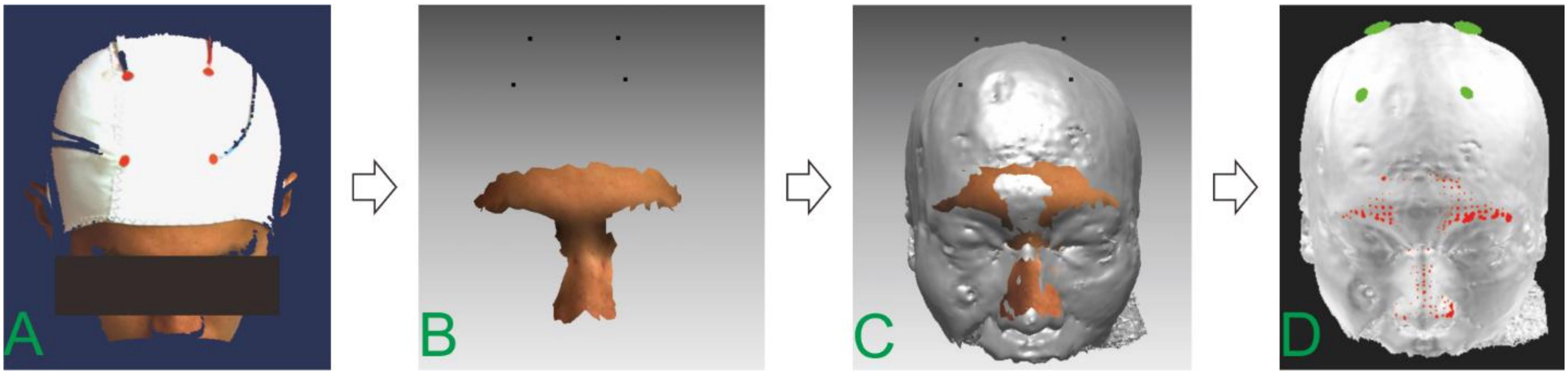
・ Due to hand operation, it takes longer time.

Co-registration 4, 3D camera



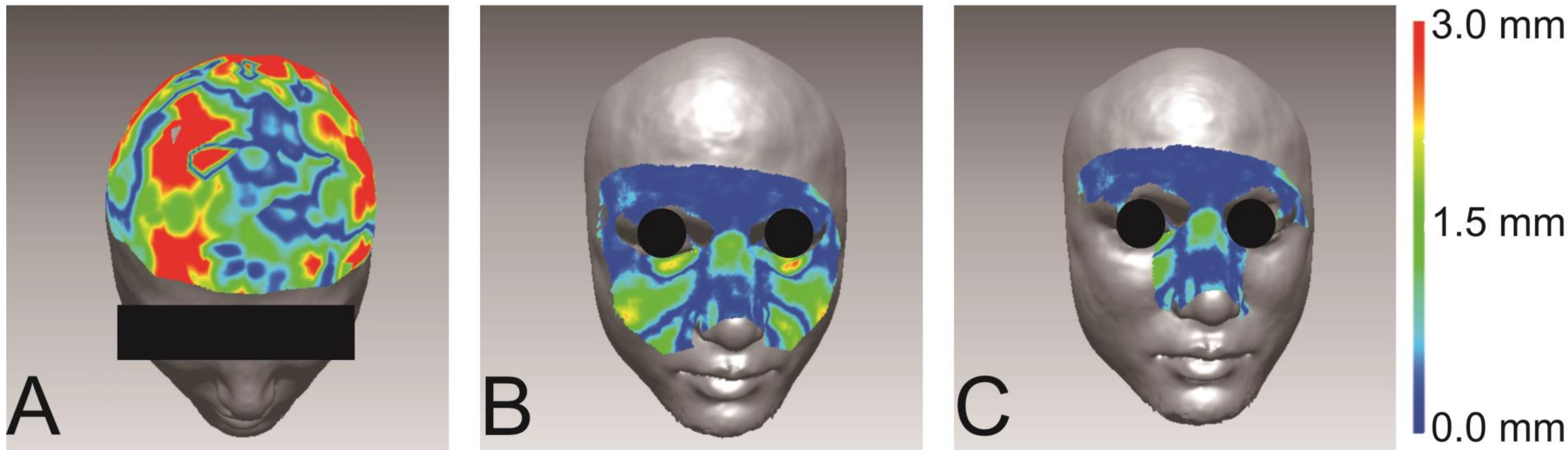
・Non-contact type, therefore measurement ends instantaneously with keeping very high resolution.

Co-registration 5, A way of co-registration using 3D camera



Schematic flow-chart of the co-registration process using a 3D-camera. Original snapshot (A). Four marked HPIs (black dots) and the face after removing the areas covered by the cap and unstable cheek region (B). Registration with the MRI contour (C). Imported into the MNE tool (D). The cap shown in (A) is commonly used for transcranial magnetic stimulation (TMS) experiments to mark the stimulation site for TMS.

Co-registration 6, Targer Registration Error (TRE)

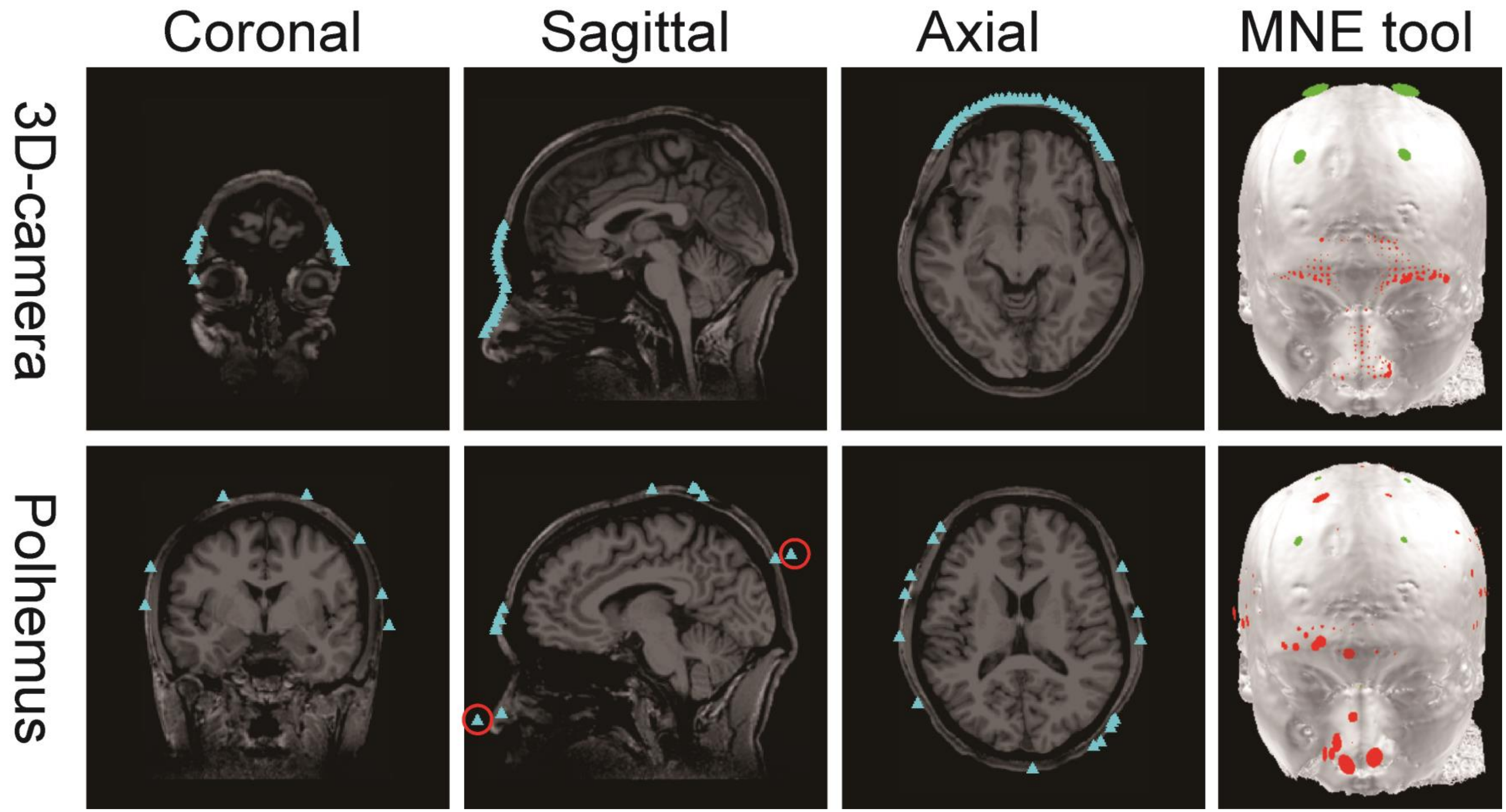


A: Results using Polhemus
TRE=2.12mm

B: Using 3D camera before eliminating the non-fitting areas
TRE=0.67 mm

C: Final results using 3D camera
TRE=0.37mm

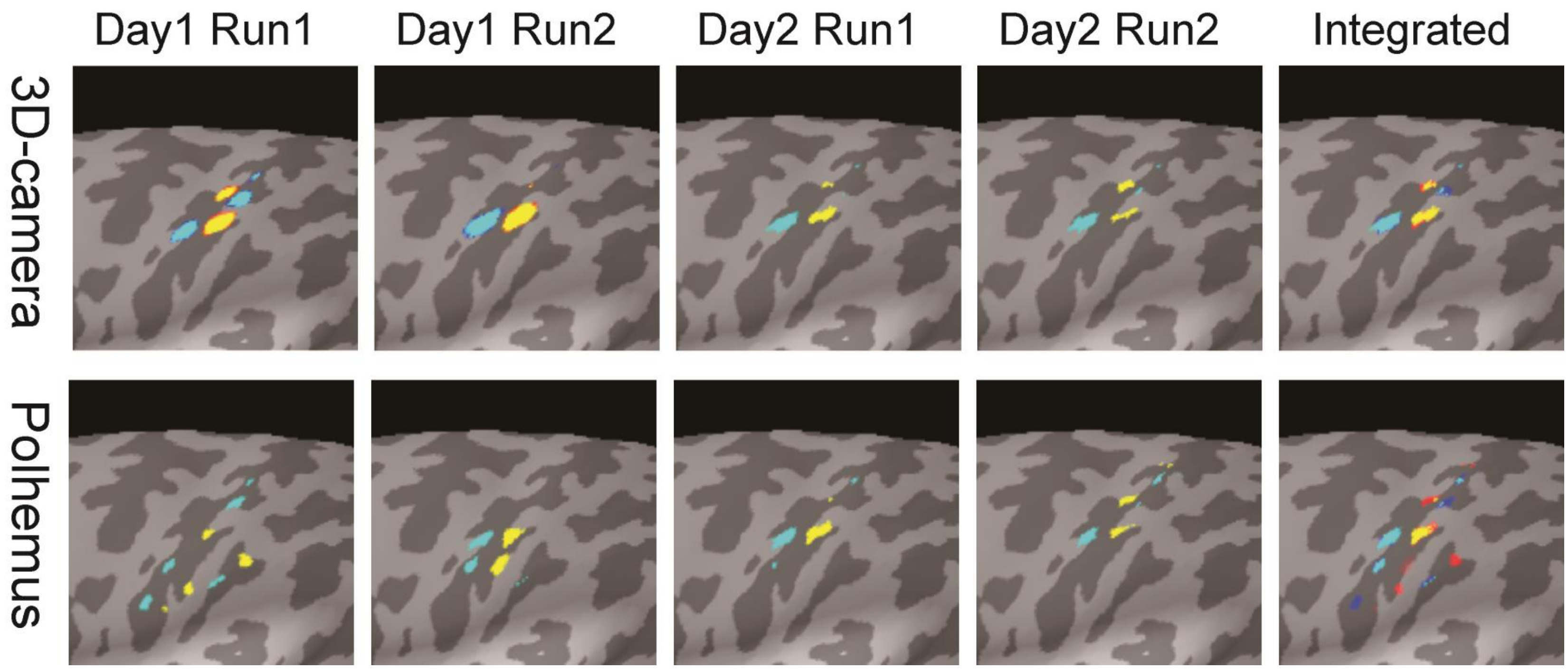
Co-registration 7, anatomical image



Obviously, the results from 3D-camera show continuous and well fitted registration to MRI contour.

In polhemus measurement, points that have jumped are marked by the red circles, while no jumped point was observed using 3D camera technique.

Co-registration 5, MNE results



・Figure shows the MNE results using tactile stimulation to right thumb on left hemisphere. Measurements were performed two runs per day and two days.

・Higher reproducibility using 3D camera is apparent.

・Also, using 3D camera, the results were not concentrated and dispersed.

Improvement of S/N ratio

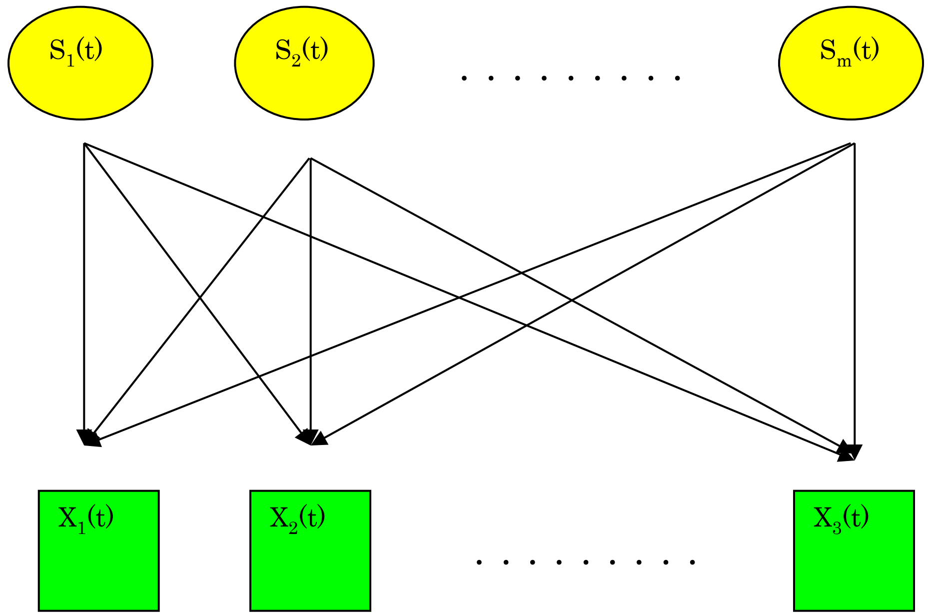
Independent Component Analysis (ICA)

ICA in general

source signal

Assume , linearly mixed

Observation



ICA
Extracting the source signals from mixed observation signals

Several algorithms have been proposed. With taking account the characteristic of signal, suit algorithm and parameter should be choice.

Major algorithms

INFOMAX -> $P(y_1, \ldots. y_n) = p(y_1) \ldots p(y_n)$ The algorithm relies on the factorization of marginal distributions.

FastICA -> Non Gaussian = independent component (Kurutosis and Negentropy (a normalized version of differential entropy) are zero for Gaussian distributions)

SOBI -> This algorithm takes into an account assumed time structure of the input signal by the joint diagonalization of correlation matrixes.

ICA & MNE

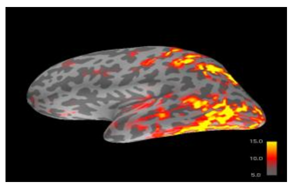
MEG observation — Separating matrix — ICs (evoked(oscillatory),epilepsy,blink,QRS and etc)

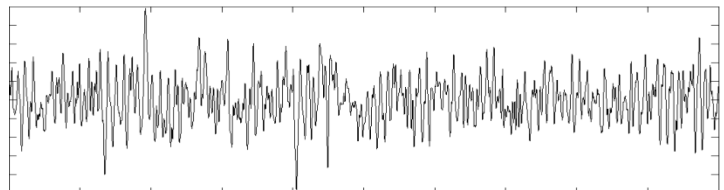
$$\begin{pmatrix} X \end{pmatrix} = \begin{pmatrix} A \end{pmatrix} \begin{pmatrix} S \end{pmatrix}$$

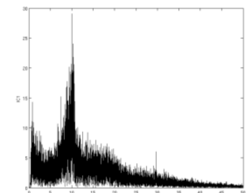
From Matrix A

From Matrix S

IC_1

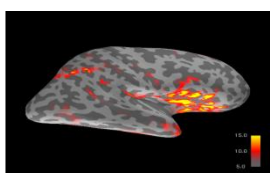


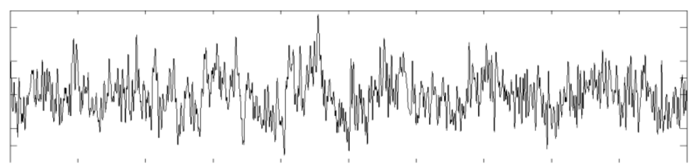


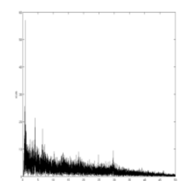


IC_n

n=number of channels







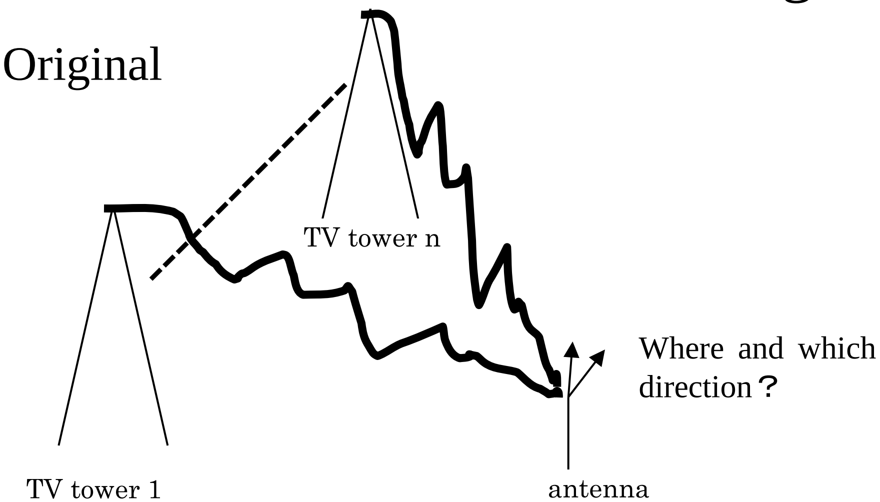
MNE for each IC — Decomposed ICs — FFT for each IC

Applying the source localization method to each column of separation matrix A , we can obtain the activation map for each IC, as well as time and space analysis for each IC.

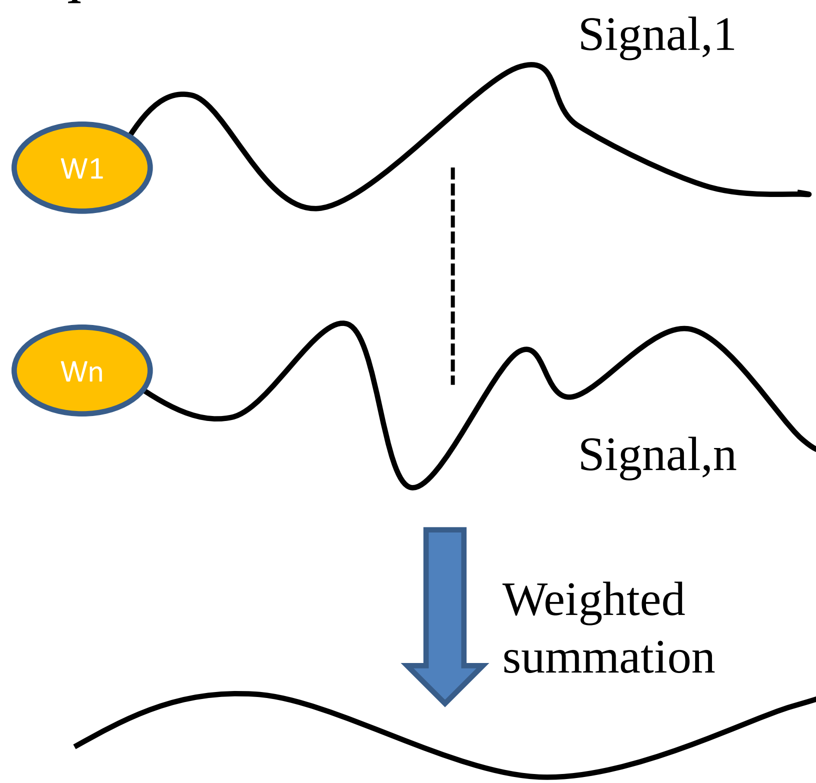
Appendix

BeamForming technique

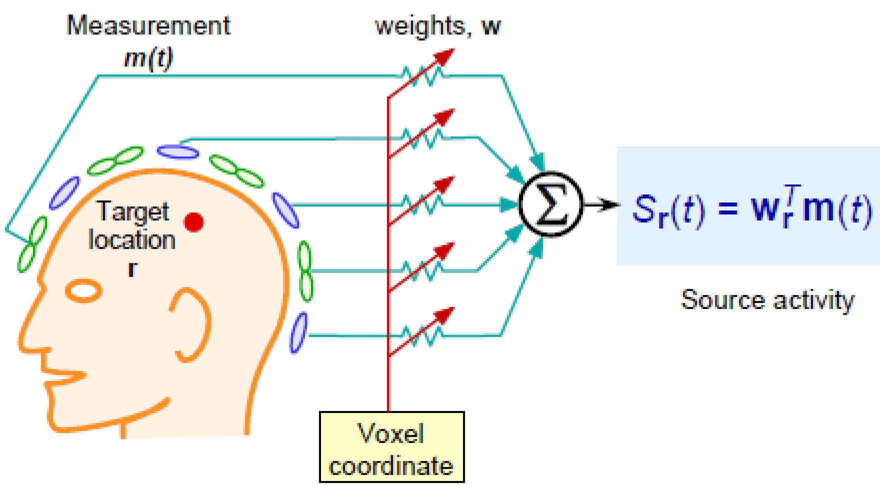
Original



Fundamental principle



Application for MEG



By changing the parameters, a variance of a signal with weighted summation should be minimized.

In MEGの, weight parameter is equivalent to the forward solution