Whole-brain time-frequency analysis of event-related potentials for the assessment of pharmacodynamic effects in the human brain

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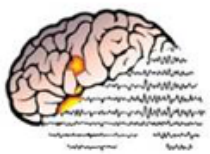
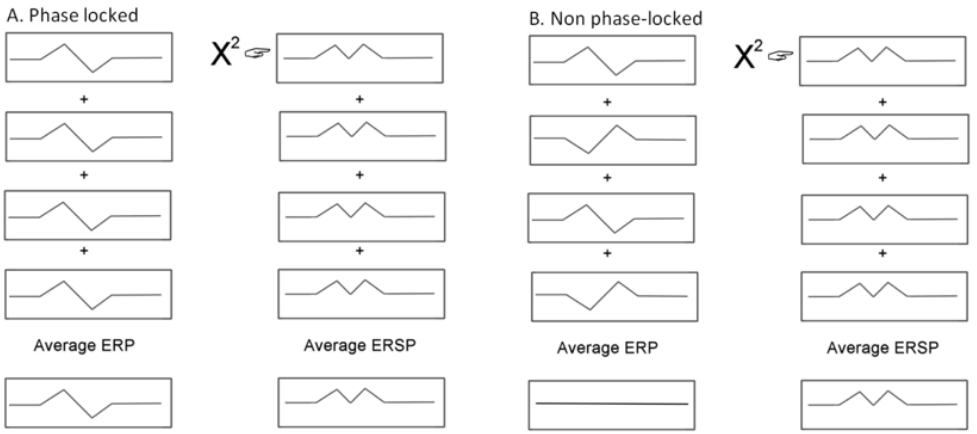
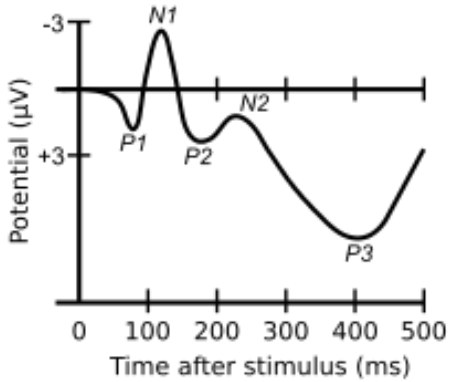


Whole Brain Time-Frequency Analysis (WBTF)

- WBTF measures change in evoked and induced event-related brain activity (ERBA)
- WBTF focuses on changes in fast sensory and later cognitive components of phase-locked even-related potentials (ERP) and *not* phase-locked event-related spectral perturbation (ERSP) Currently proprietary designed and recorded ERBA tasks include visual or auditory P300, MMN, CDA and N2pc.

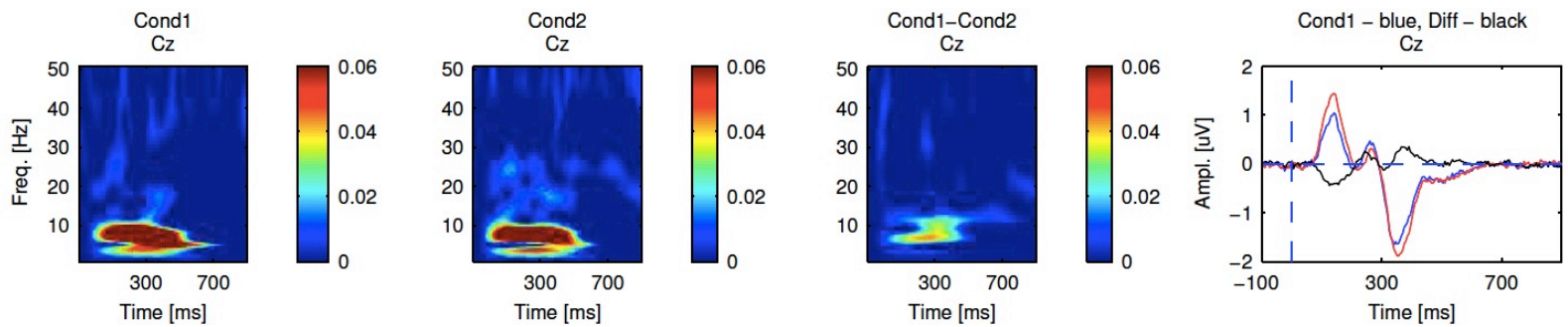




Picture taken from Wikipedia:
`https://en.wikipedia.org/wiki/Event-related_potential`.

Whole Brain Time-Frequency Analysis (WBTF)

- Selected evoked (ERP) and induced (ERSP) measures are computed on time-frequency transformed trials
- WBTF is designed to compare the whole brain differences between two conditions/sessions
  - between pre-dose baseline and post-dose tests
  - between sessions of drug treatment
  - between baseline and post-traumatic tests
- Focus on individuality; responders vs. non-responders, progression

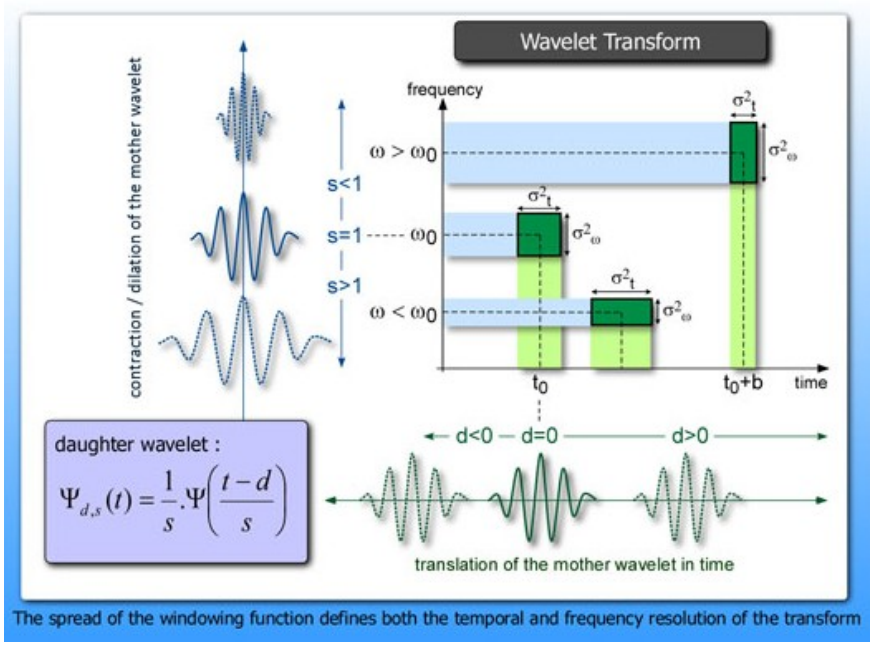


Example of the evoked measure computed at the electrode Cz for Cond1 and Cond2 and their difference .

WBTF procedure steps

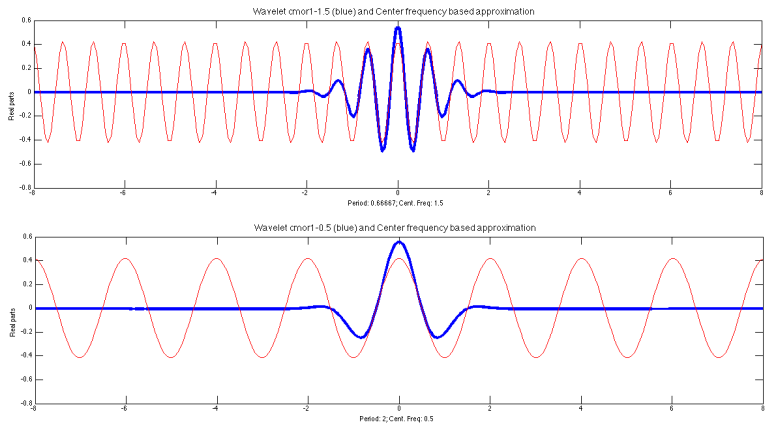
1. EEG to ERP pre-processing; re-sampling, re-referencing, filtering, artifacts processing, segmentation, baseline correction, etc.
2. Continuos Wavelet Transform (CWT); applied to each ERP trial

$$cwt(s,d;f(t),\Psi(t)) = \int_{-\infty}^{\infty} f(t)\frac{1}{\sqrt{s}}\Psi^*(\frac{t-d}{s})dt$$

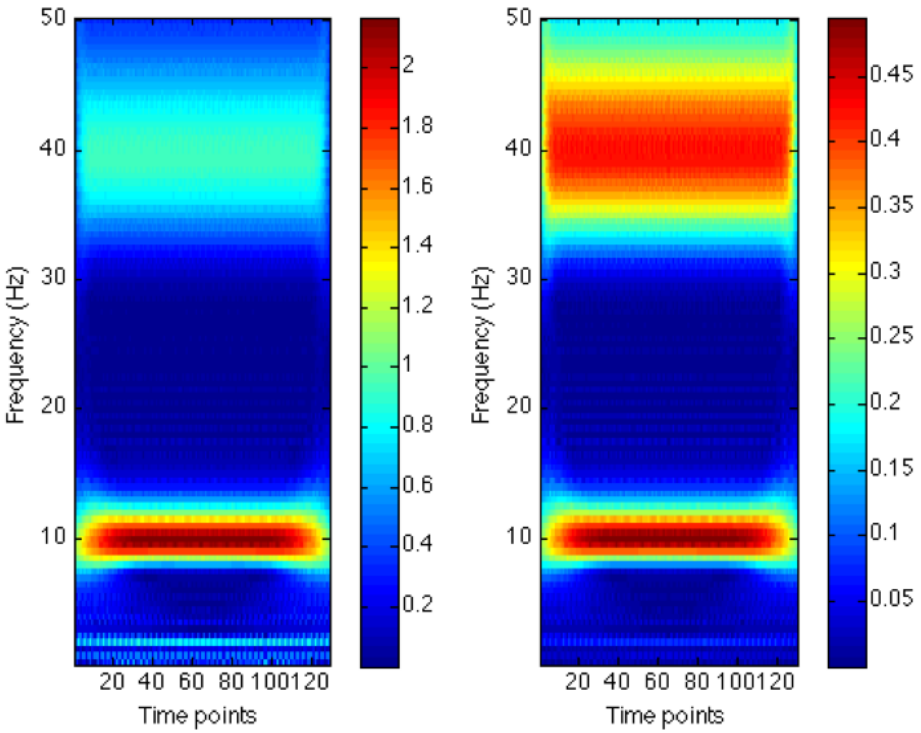


Picture taken from NOCIONS lab web page:
`http://www.nocions.org`.

Morlet wavelets (*cmor1-0.5* or *cmor1-1.5*); center freq. $f_c = 0.5$ or 1.5 Hz, $f = f_c/s$



3 Energy normalization; to equalize $|cwt(s, d)|$ mag. over scales, EEG signal at higher frequency bands has typically less power and we focus on differences over the whole time-frequency plane



Example of the energy normalization effect. Signal consisting of 2 sinusoidal waves at freq. 10 Hz and 40 Hz was transformed by CWT (cmor1-1.5)

4 Compute WBTF measures

Evoked activity measures

i) Time-frequency transformed evoked potential

$$avWT(c,f,t) = \frac{1}{N}\sum_{n}^{N} cwt(c,f,t,n)$$

ii) Inter trial phase coherence

$$ITPC(c,f,t) = \frac{1}{N}\sum_{n}^{N} \frac{cwt(c,f,t,n)}{|cwt(c,f,t,n)|}$$

iii) Inter trial linear coherence

$$ITLC(c,f,t) = \frac{1}{N}\sum_{n}^{N} \frac{cwt(c,f,t,n)}{\sqrt{\frac{1}{N}\sum_{n}^{N}|cwt(c,f,t,n)|^2}}$$

4 Compute WBTF measures

Induced activity measures

i) Induced power

$$Induced_{pwr}(c,f,t) = ERSP(c,f,t) - |avWT(c,f,t)|^2$$

$$ERSP = \frac{1}{N}\sum_{n}^{N} |cwt(c,f,t,n)|^2$$

ERSP - evoked spectral perturbation

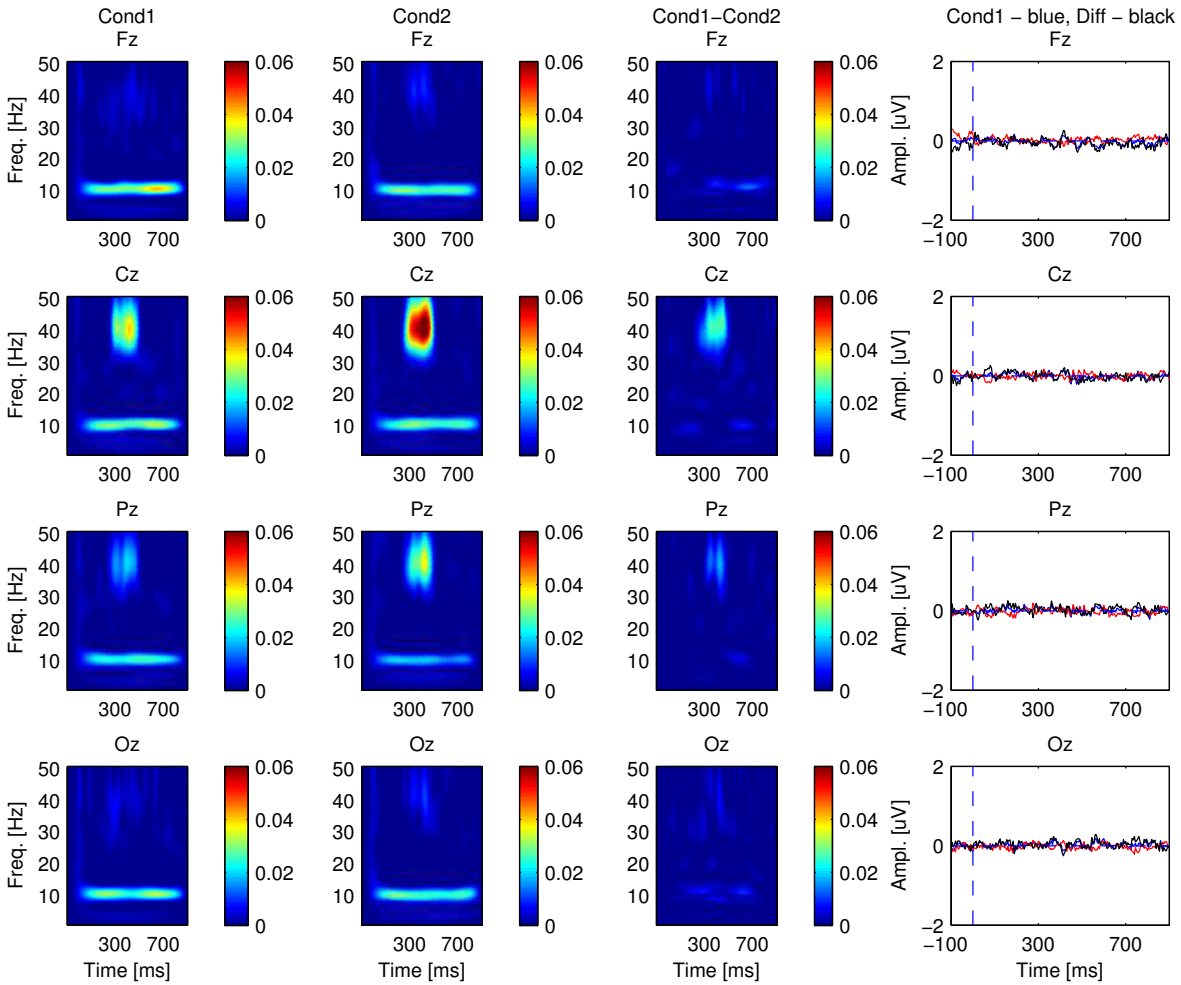
ii) Induced magnitude

$$Induced_{mag}(c,f,t) = WTav(c,f,t) - |avWT(c,f,t)|$$

$$WTav = \frac{1}{N}\sum_{n}^{N} |cwt(c,f,t,n)|$$

c-channel, f-frequency, t-time, n-trial/epoch

WBTF procedure steps



Example of the Induced$_{pwr}$ (c,f,t) WBTF measure

5 **Compute the WBTF measure differences**
for every time-frequency point compute a difference between Cond1 and Cond2 values of the given WBTF measure

6 **Baseline correction of the WBTF measure differences**
pre-stimulus time activities are subtracted from post-stimulus

7 **Cumulative difference over electrodes**
differences are summed over all electrodes or over selected spatial patches

8 Estimate significance of differences

Permutation testing

i) Permute Cond1 and Cond2 trials

ii) Construct permutation distribution (PD)

iii) Estimate significance of differences at each time-frequency point

iv) Correct for multiple comparisons testing

Nichols TE, Holmes AP, Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping, 2002 Jan;15(1):1-25.

9 Compute WBTF scores

WBTF scores

i) Significance score: $S_{t,f} = -\log_{10}(1 - p_{t,f})$

Example:

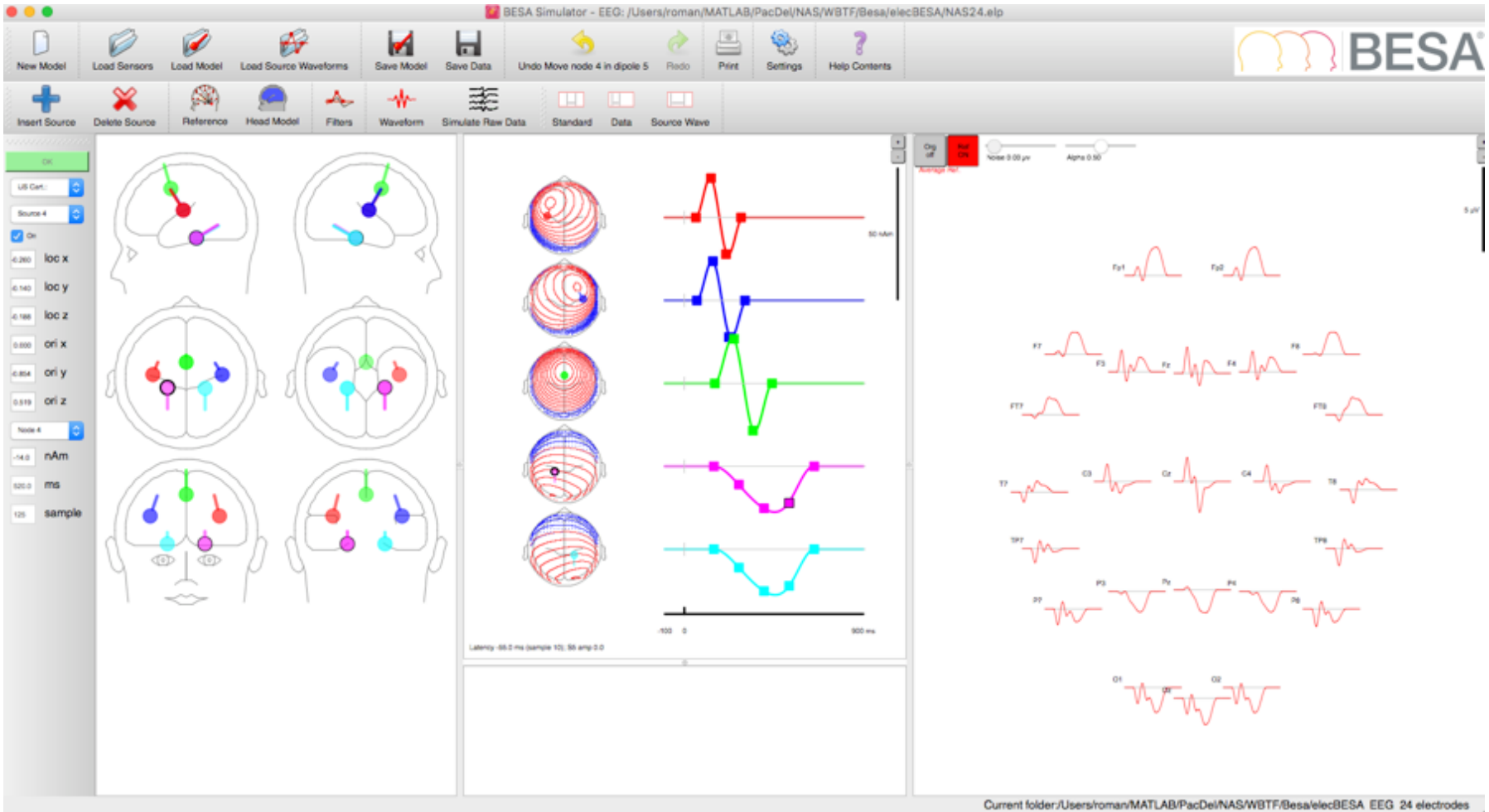
$$S_{t,f} = -\log_{10}(1 - .99) = -\log_{10}(.01) = 2$$

$p_{t,f} = 0.01$ means that $WBTF(t, f)$ is 99/100 times greater than the considered PD

ii) Total score: for each WBTF measure sum $S_{t,f}$ over all post-stimulus t, f points

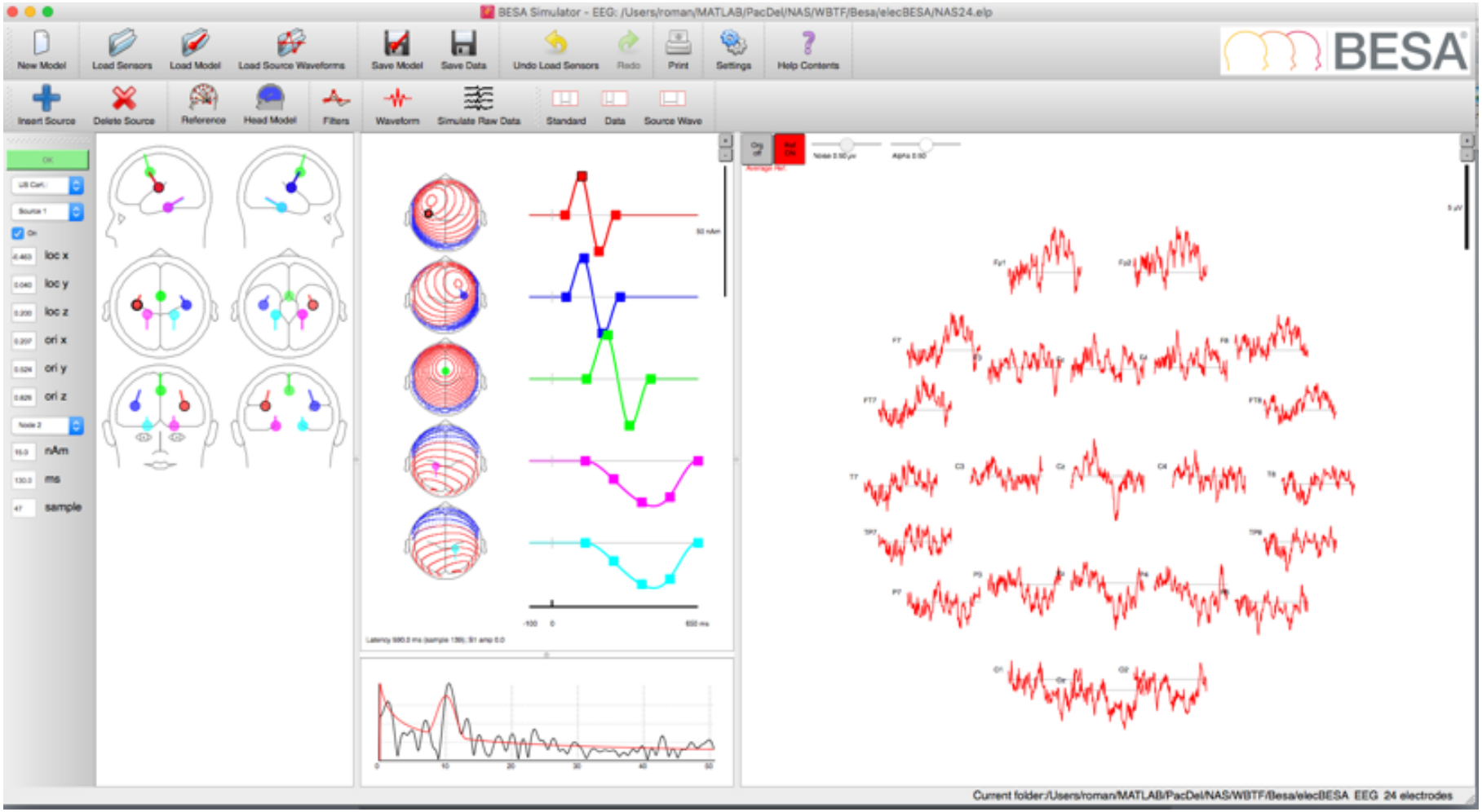
iii) Composite WBTF score: combine scores by taking the maximum significance at a given t, f point over all WBTF measures

BESA Simulator - evoked components



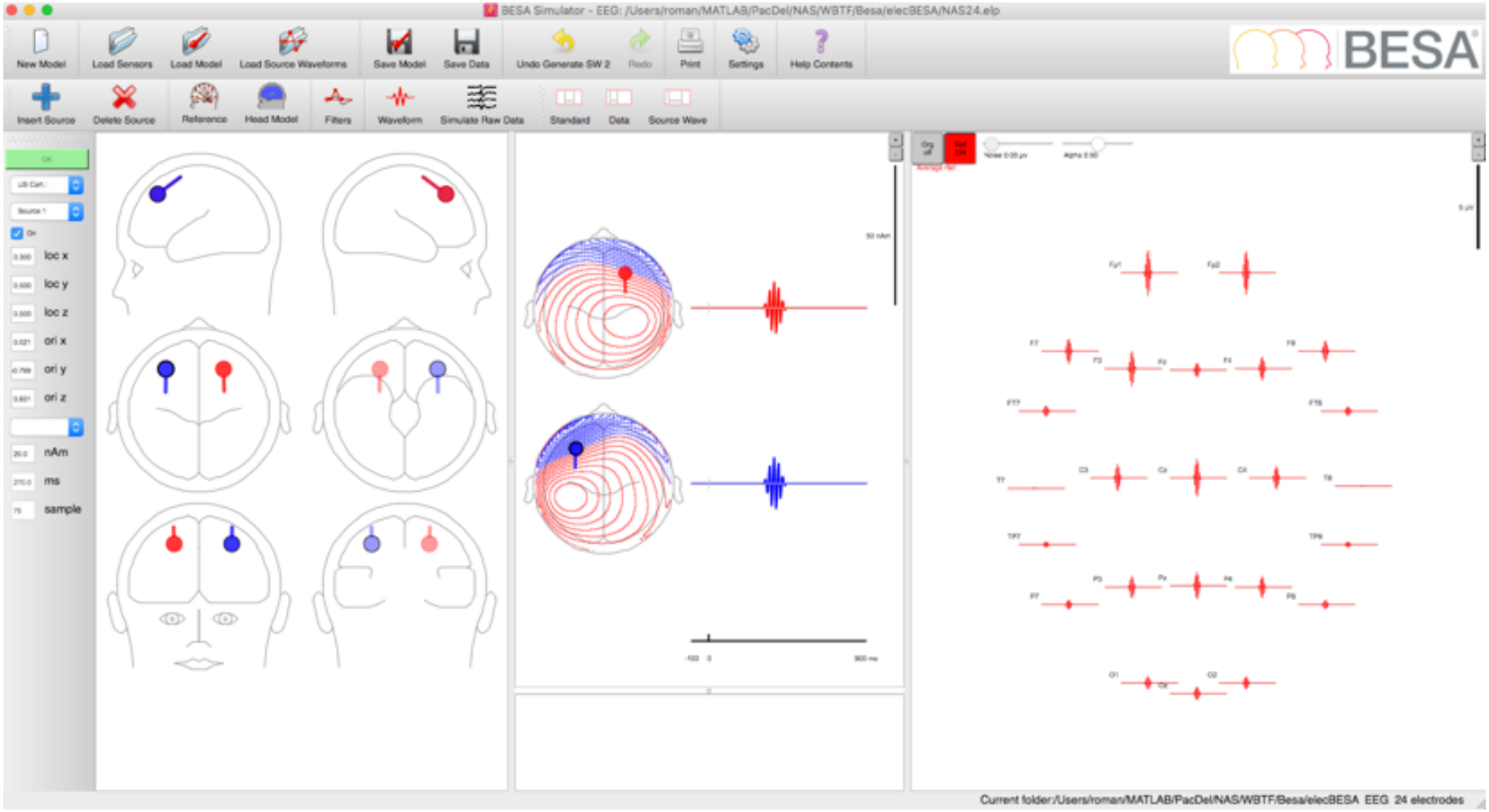
Sample of evoked sources modelling N1 and P3b event-related components

BESA Simulator - evoked components



Sample of background EEG (noise) added to the pervious N1P3b model

BESA Simulator - induced components



Sample of the two induced oscillatory sources both at the level of 10nA / 40 Hz

General parameters:

- 24 electrodes following the NAS system setting
- 100 trials for each condition, sampling rate 200Hz
- time interval -200 to 900 ms, 100 ms baseline mirrored
- EEG samples were i) same or ii) different for two conditions

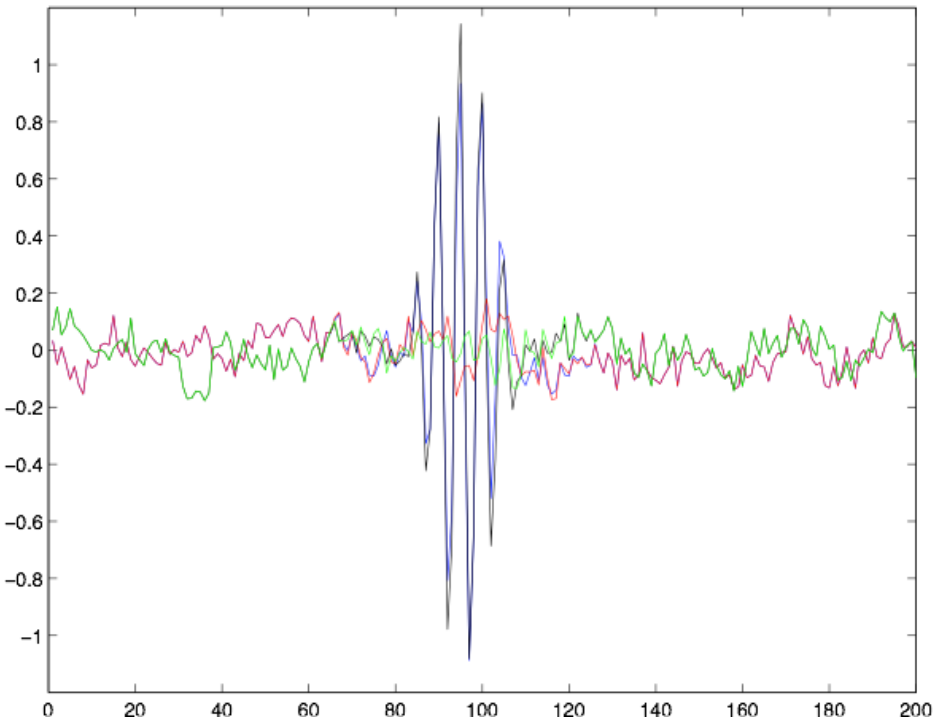
Evoked sources:

- 5 cortical sources modelling N1 and P3b event-related components
- three models with different amplitudes of cortical sources

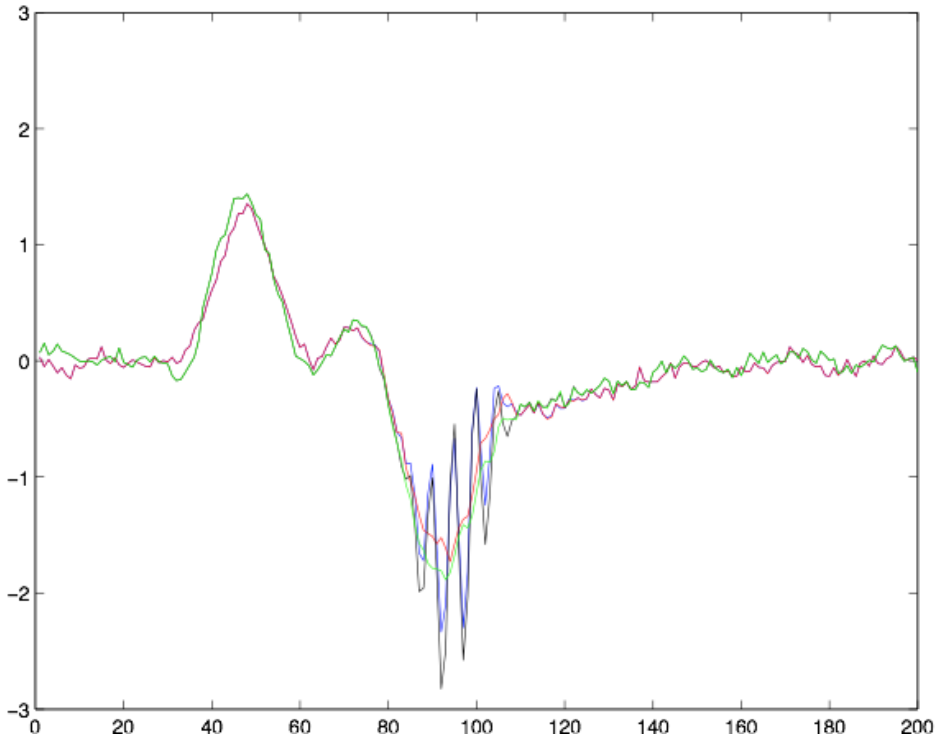
Induced sources:

- 2 symmetrical induced sources at 40 Hz, sinusoidal wave with Hamming window
- four models with amplitude levels of 5, 8, 9,10 nA
- duration 300 to 450 ms, beginning randomly set 200-400 ms post-stimulus

Sample ERSP and ERP

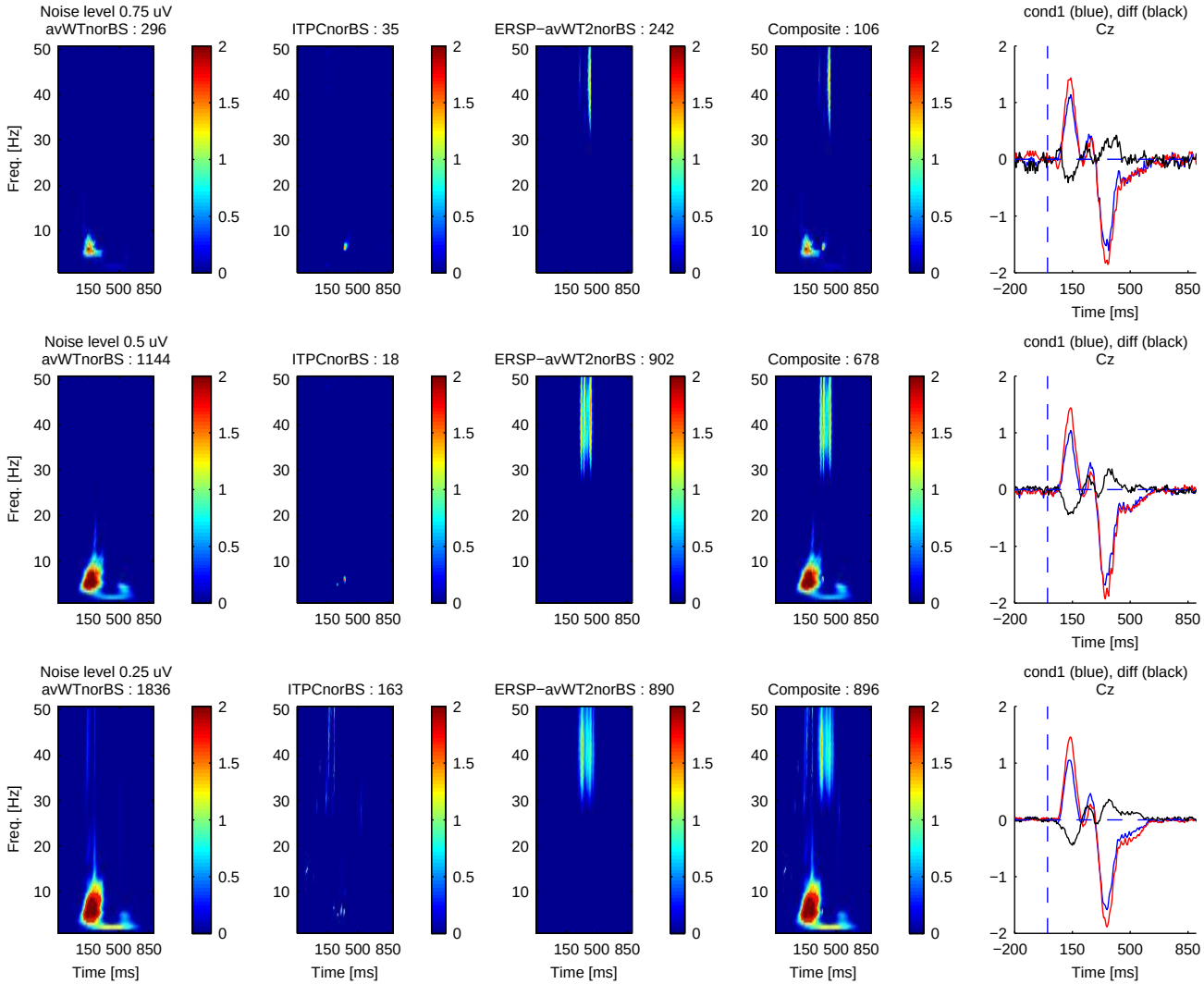


Sample of averaged ERSP at Cz with jittered (red, green) and not jittered (blue,black,) induced sources. Sources 9nA (blue) and 10nA (black). Noise level 0.75uV and alpha proportion of 0.5.



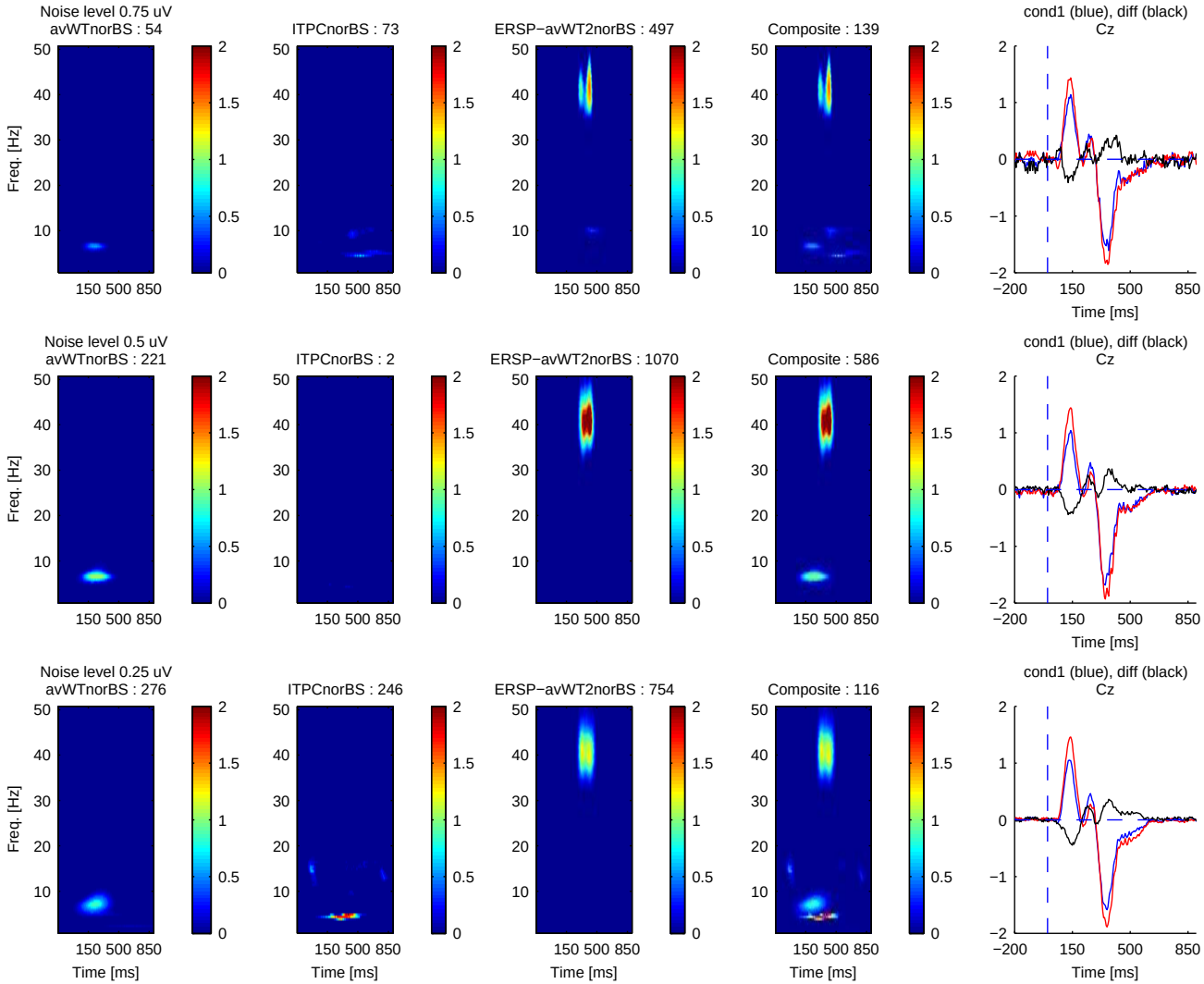
Sample of averaged ERP and ERSP at Cz. ERSP sources jittered (red, green) and not jittered (blue8nA, black10nA) induced sources . ERP sources: model2 ERP (red), model1 ERP (green). Noise level 0.75uV and alpha 0.5.

Results



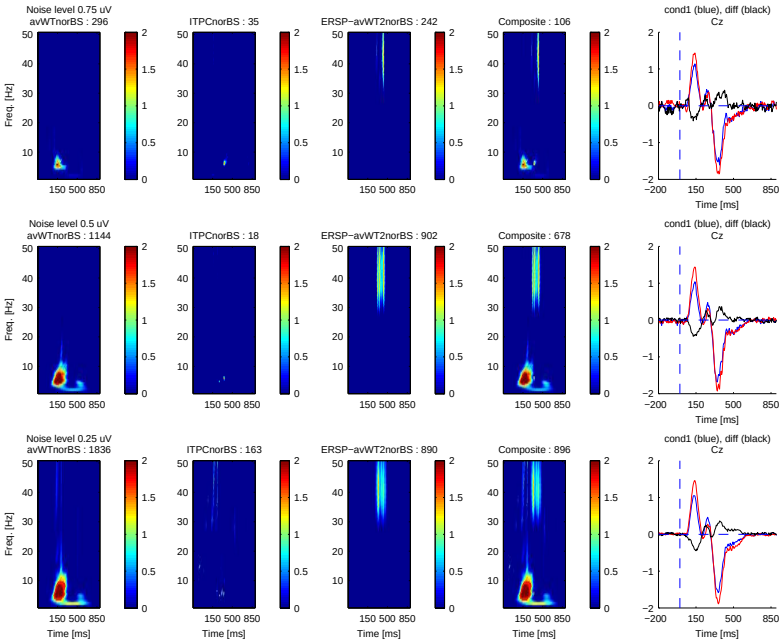
Results for cmor1-0.5.

Results

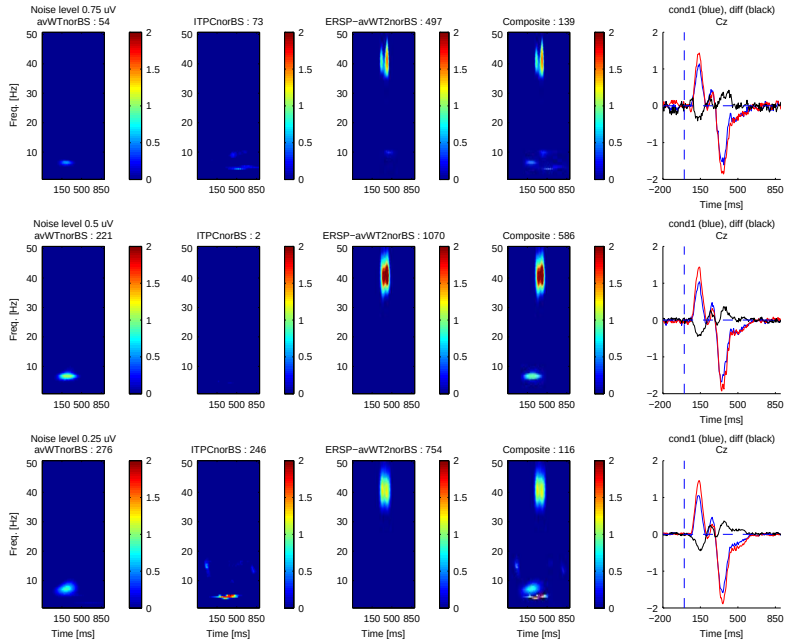


Results for cmor1-1.5.

Results



Results for cmor1-0.5.



Results for cmor1-1.5 .

Conclusions from analyzed simulation and clinical studies data

- Using the approach we analyze a wide collection of data from:
  - several pharmaco-clinical studies
  - traumatic brain injury (TBI) studies, diagnosing concussion and its progression
- We found that:
  - WBTF is sensitive to small evoked (ERP) and induced (ERSP) changes
  - CWT with different time-frequency resolution can be beneficial
  - Correction of multiple comparison testing should be considered
  - Statistical significance testing of the total composite and individual WBTF scores is still needed