Time/Frequency Analysis Methods in Translational Research

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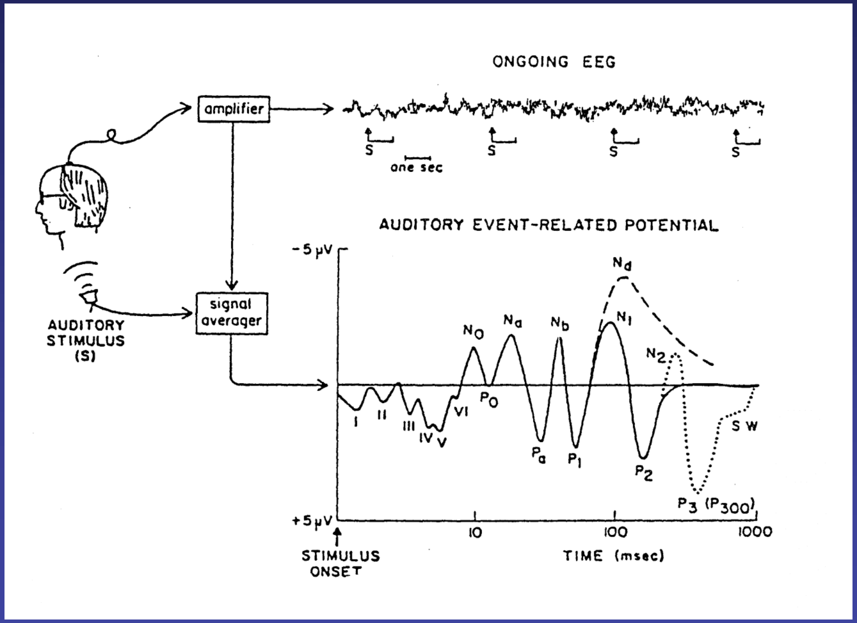
Overview

- What is time/frequency (T/F) analysis?
  - ERP vs. EEG analysis
  - T/F methods
  - Survey of applications
- What can T/F analysis tell us about schizophrenia?
- Issues in utilizing T/F analyses
- Future directions

ERP view of the EEG

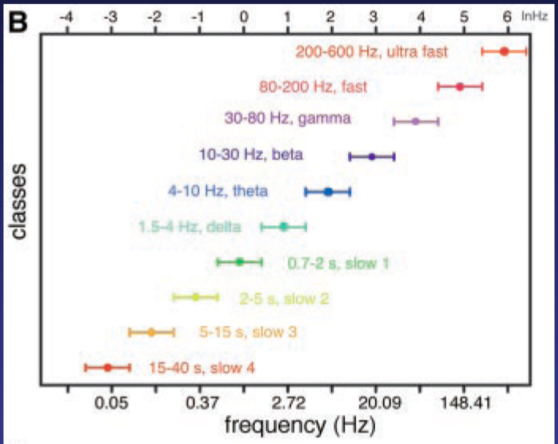
- Event-related brain potentials (ERPs)
  - Transient patterns of brain activity that reflect various kinds of processes.
  - Derived by averaging signals (time domain analysis).
  - Activity not phase-locked to the event of interest is canceled out.
- Non-ERP portion of signal (“background”) is considered “noise”.

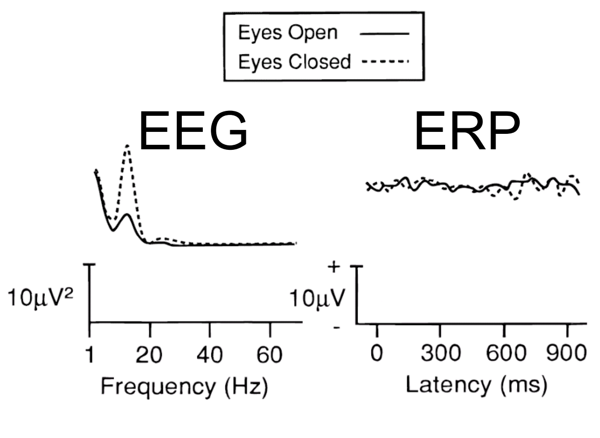


Classical EEG

- But is the rest of the EEG really noise?
- Ongoing EEG rhythms identified before ERPs.
- Frequency bands
  - Delta (δ): 1-4 Hz
  - Theta (θ): 4-8 Hz
  - Alpha (α): 8-13 Hz (also μ)
  - Beta (β): 13-30 Hz
  - Gamma (γ): 30-100 Hz
  - Also infraslow (<1 Hz), high γ (>100 Hz)
- Analyzed in the frequency domain.
  - Linked to states of arousal/consciousness.
  - Relevant in sleep research, clinical neurology.
  - But not successfully linked to cognitive processes.

Buzsaki & Draguhn (2004, *Science*)



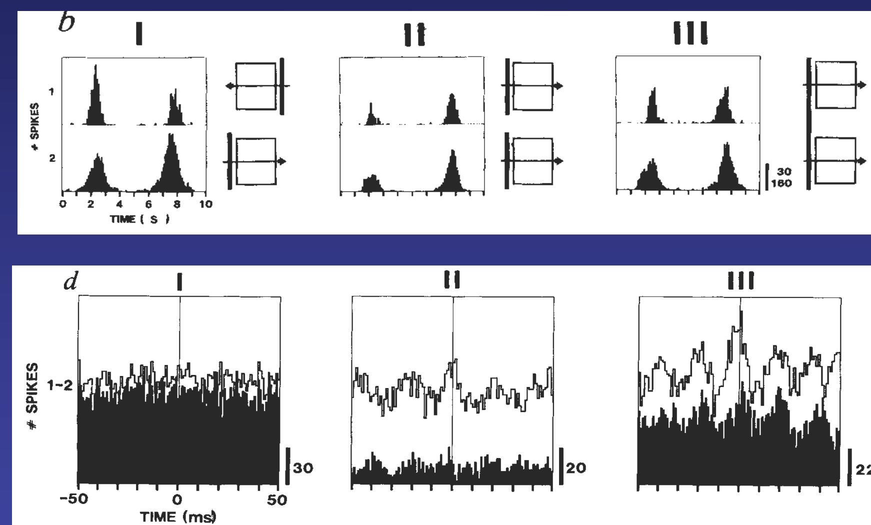


Spencer & Polich (1999, *Psychophysiol*)

Modern view of the EEG

- ERP approach highly successful for studying cognition.
- But what about that "background noise"?
  - Some evidence that pre-stimulus EEG phase/power is correlated with post-stimulus ERPs (e.g., Sayers et al., 1974; Jasiukaitis & Hakerem, 1988).
  - Oscillations may play important role in information coding (e.g., Eckhorn et al., 1988; Gray et al., 1989; O'Keefe & Recce, 1994).

Gray et al. (1989, *Nature*)

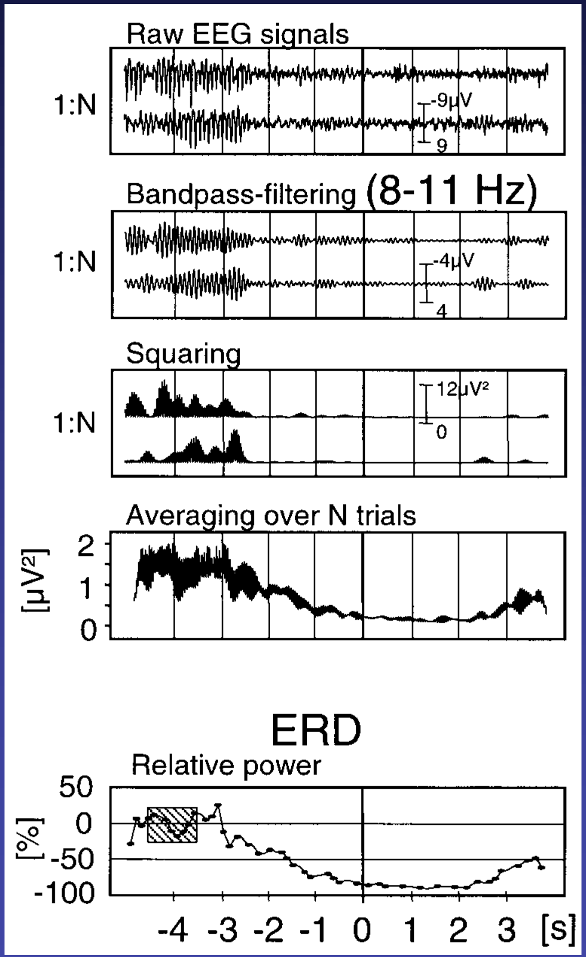


T/F analysis

- Measuring event-related changes in the frequency domain.
- “Background” EEG may contain oscillations not strictly phase-locked to stimulus presentation.
  - These oscillations may be related to cognitive processes (just as ERPs).
- T/F methods may also reveal stimulus-locked oscillations not seen in the ERP.

T/F methods

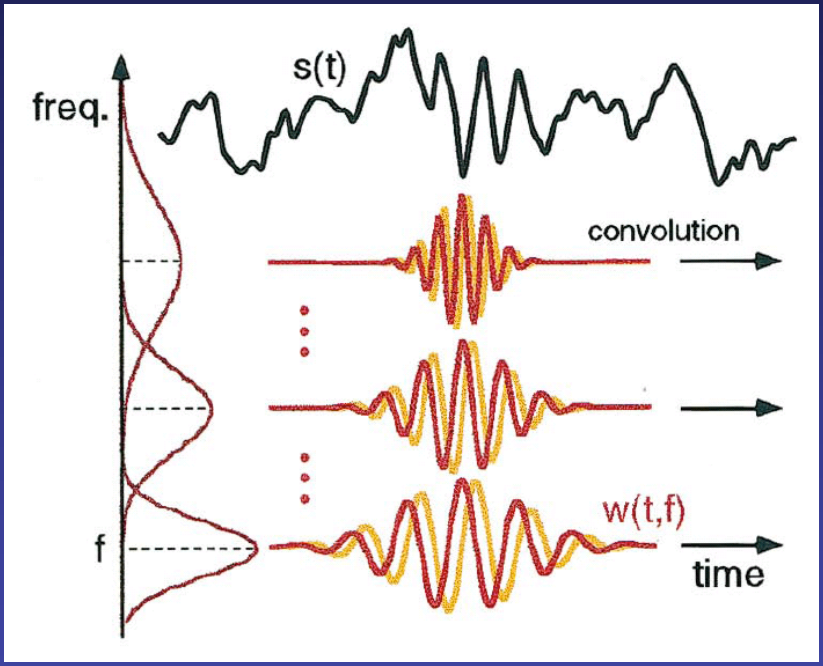
- Band-pass filter the EEG.
  - Computationally inexpensive.
  - OK if frequency band of interest known *a priori.*
  - Otherwise hard to determine the bandwidth of an oscillation.
  - Can't do phase analyses.



Pfurtscheller & da Silva (1999, *Clin Neurophysiol*)

T/F methods

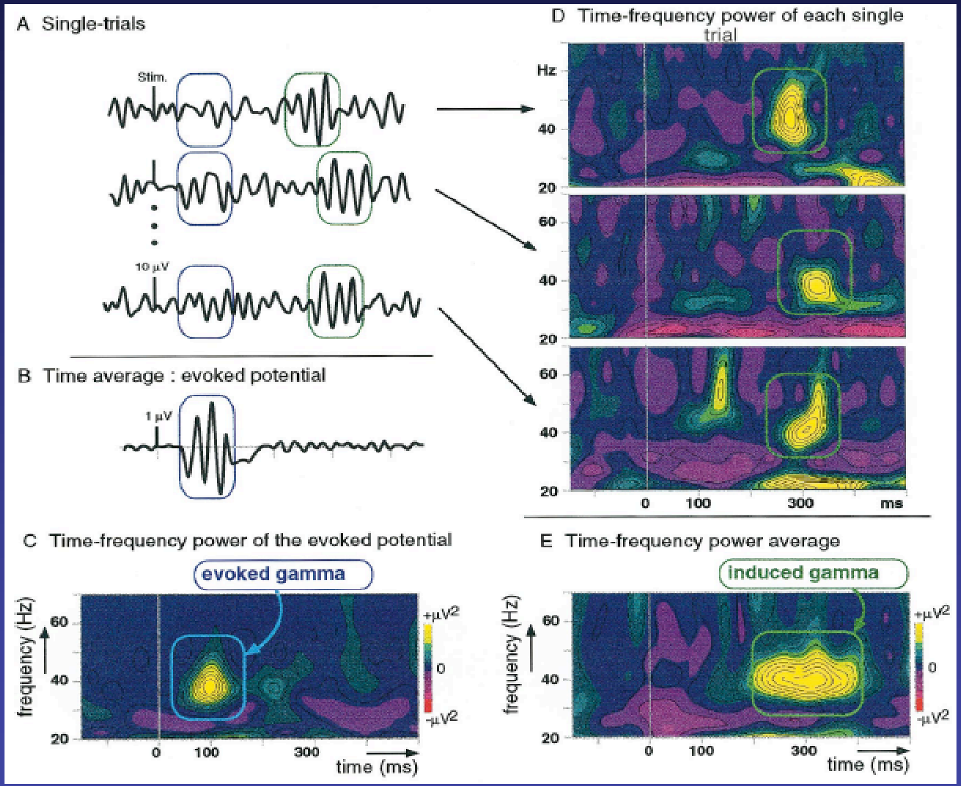
- Windowed Fast Fourier Transform (FFT), wavelets allow assessment of whole spectrum.
- Windowed FFT
  - Applied in short windows across the EEG epoch.
  - Fixed epoch length not ideal for all oscillation frequencies.
  - T/F tradeoff:
    - Improving time resolution (shorter window) leads to poorer frequency resolution (wider freq bin), & vice versa.
- Wavelet techniques (Morlet)
  - Designed for T/F decomposition, detecting transient signals.
  - T/F tradeoff scales with frequency.
    - Low frequencies have longer wavelets, high frequencies have shorter wavelets.



Tallon-Baudry & Bertrand (1999, *Trends Cogn Sci*)

What can T/F methods detect?

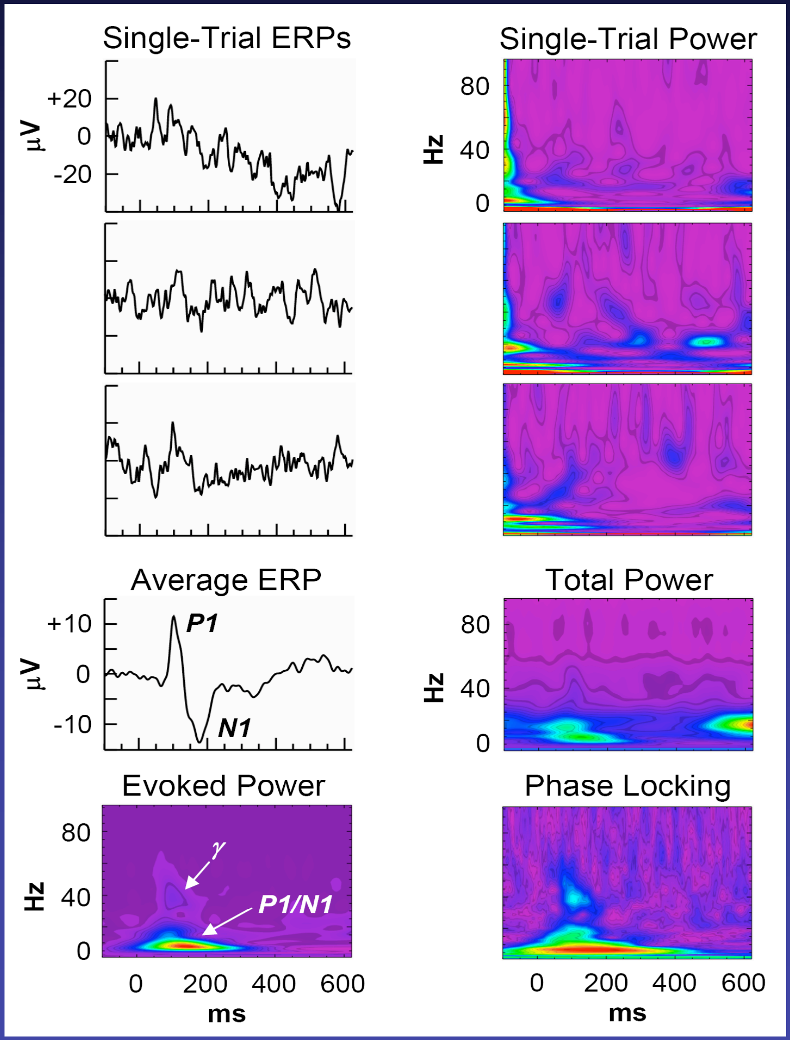
- 2 basic kinds of activity:
  - Evoked
    - Phase-locked to event of interest (e.g., stimulus onset).
  - Induced
    - Event-related but not strictly phase-locked to event.
- Both transients (ERPs) and oscillations are detected.
  - Hard to tell apart.



Tallon-Baudry & Bertrand (1999, *TICS*)

Event-related spectral measures

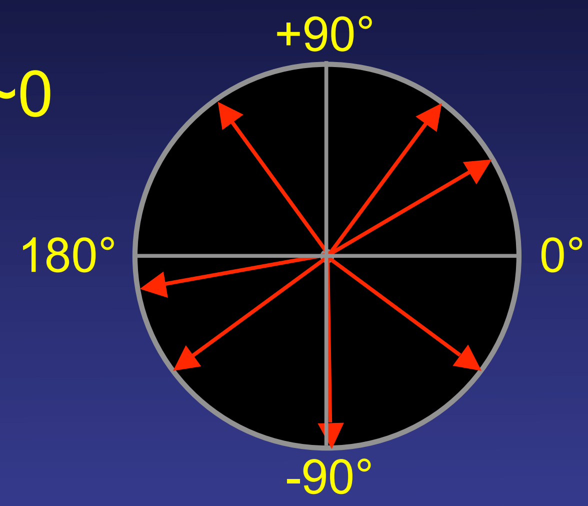
- Evoked power
  - Computed from average ERP.
    - Non-stimulus locked activity is averaged out.
  - Includes ERPs, stimulus-locked oscillations.
- Total power
  - Average of single-trial power spectra.
  - Non-stimulus locked activity is preserved.
  - Includes induced and evoked responses.
- Phase synchronization



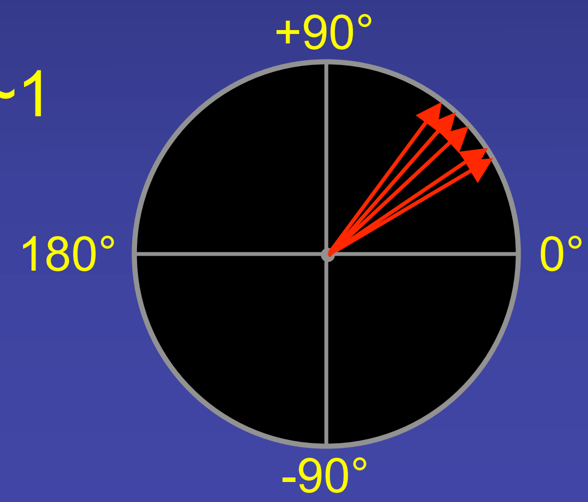
Phase synchronization

- Many names for same measure:
  – Phase locking factor (PLF)
  – Phase locking value (PLV)
  – Inter-trial coherence (ITC)
- Amplitude-independent
- Based on variance of phase across trials.
  – 1 minus circular phase variance
  – 0 = random distribution
  – 1 = perfect synchronization

PLF = ~0



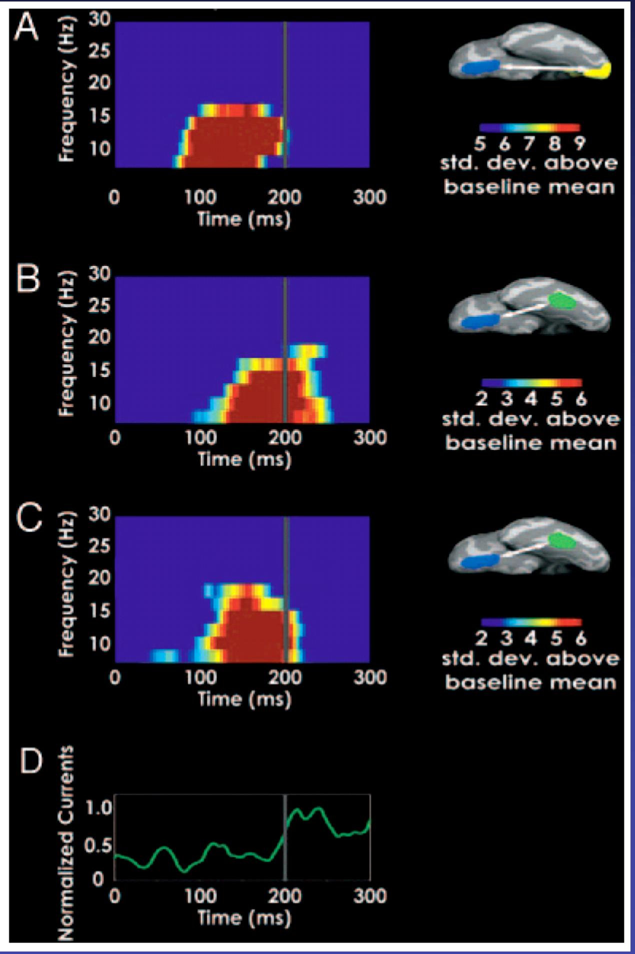
PLF = ~1



Functional connectivity

- Phase synchronization can be computed between EEG/MEG sensors or brain sources.
- Computed on phase lags between sensors/sources.

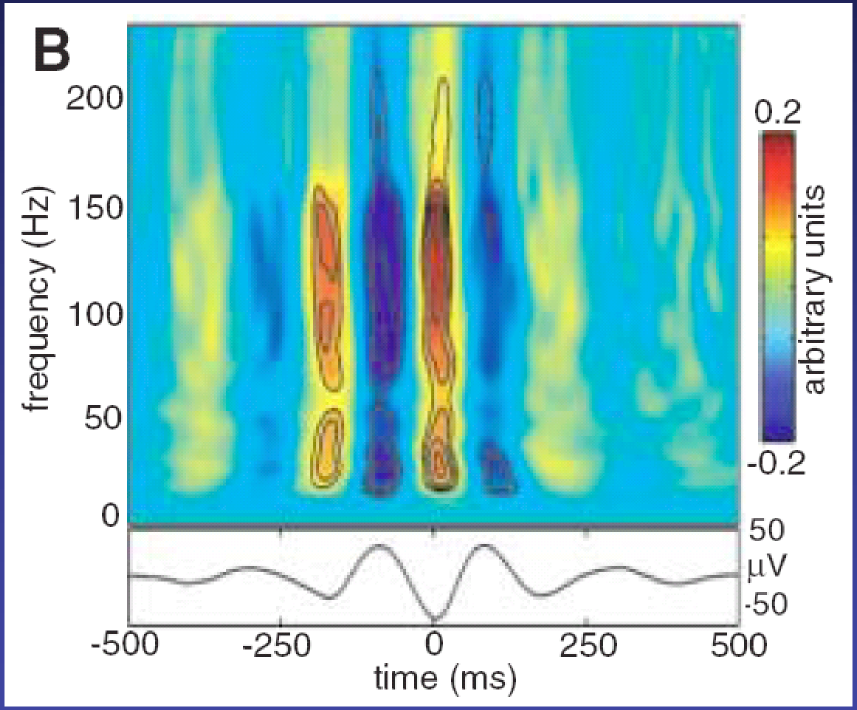
Bar et al. (2006, *PNAS*)



Cross-frequency interactions

- Rhythms are organized hierarchically.
  - Not just hippocampus but neocortex too.
- Low frequency oscillations (δ, θ) can modulate the power/phase of higher-frequency oscillations (β, γ).

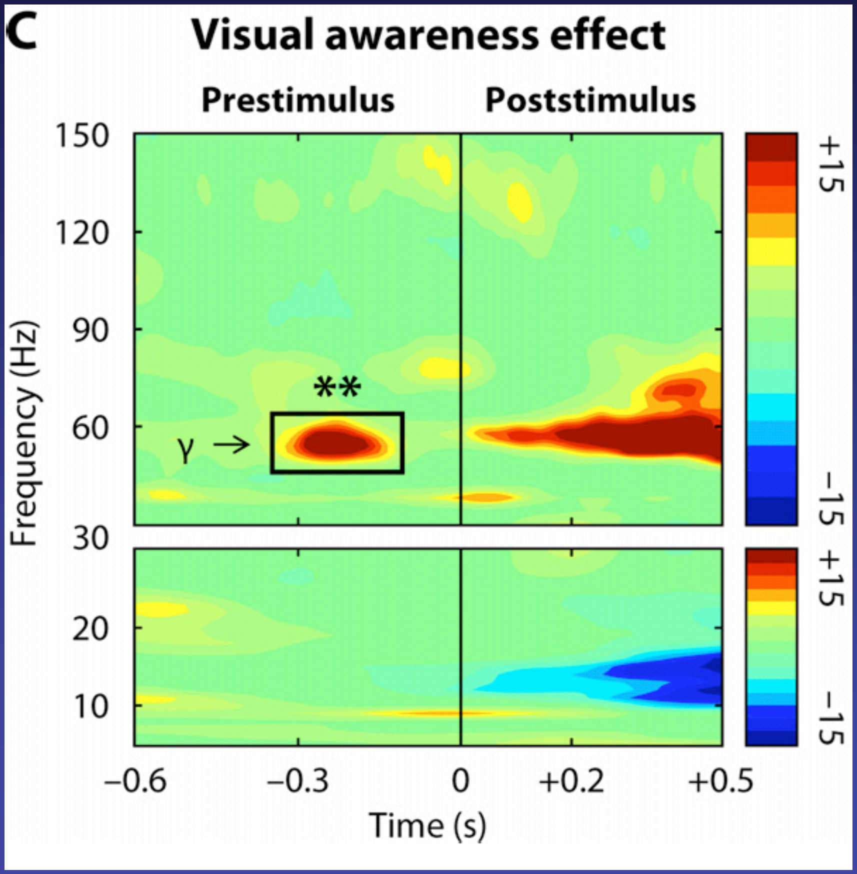
Canolty et al. (2006, *Science*)



State dependence of cognitive processes

- Power and phase of pre-stimulus oscillations can influence perception.

Wyart & Tallon-Baudry (2009, *J Neurosci*)



Overview

- What is time/frequency (T/F) analysis?
- What can T/F analysis tell us about schizophrenia?
  - Why study oscillations in schizophrenia?
  - Survey of γ findings
  - Pharmacological effects
- Issues in utilizing T/F analyses
- Questions and future directions

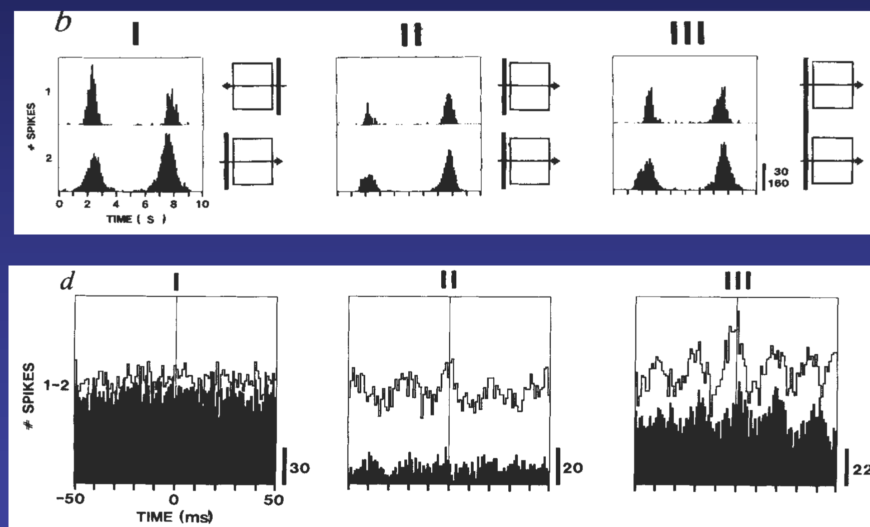
Oscillations and Schizophrenia

- Bleuler (1911)
  - “splitting of the psychic functions”
- Modern view
  - Psychological dis-integration due to failure to integrate neural circuits.
    - Widespread gray matter reductions, micro- and macroscopic connectivity abnormalities.
- Why study oscillations in schizophrenia?
  - Oscillations represent synchronized neural activity.
  - Metaphorical similarity: psychological/neurophysiological disintegration
  - Basic mechanisms of some oscillations known.
    - Link to neural circuit abnormalities, animal models.

γ oscillations

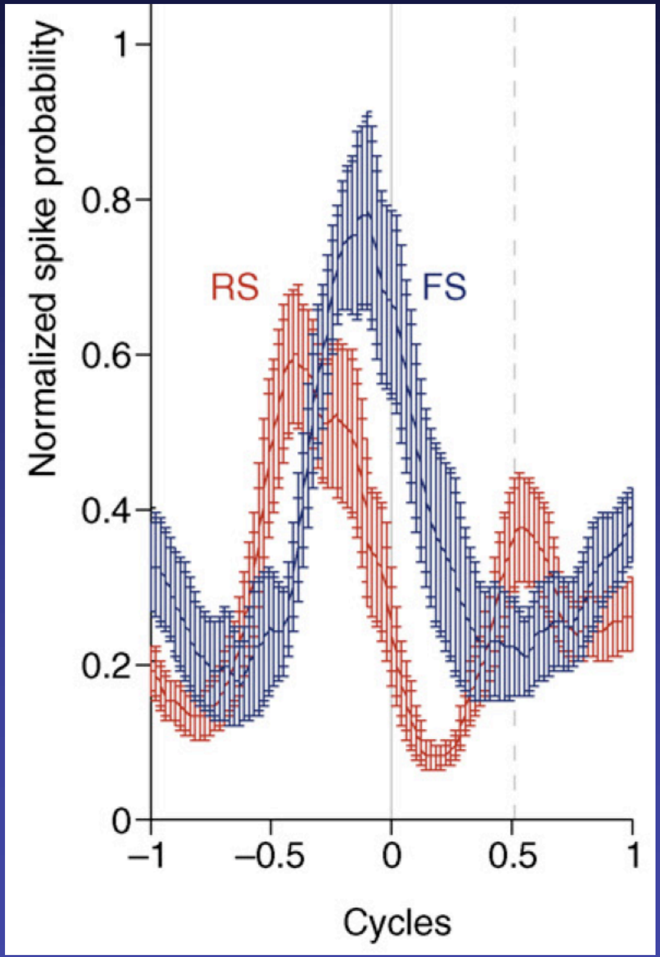
- Hebb: *cell assemblies* are basic unit of information processing in brain.
- Singer et al.: precise (ms) synchronization may link neurons into cell assemblies.
  - Mediated by γ oscillations (30-100 Hz).
  - perception, attention, memory, motor functions
- Prediction: γ oscillations abnormal in SZ.

Gray et al. (1989, *Nature*)



γ mechanisms

- γ synchronization
  - Pyramidal cells (PCs) excite inhibitory interneurons.
  - Interneurons phase output of PCs and each other.
  - Oscillation emerges from PC-interneuron interaction.
- Parvalbumin-expressing (PV+) inhibitory interneurons are critical element.
  - Fast-spiking, target perisomatic region of PCs & other interneurons.

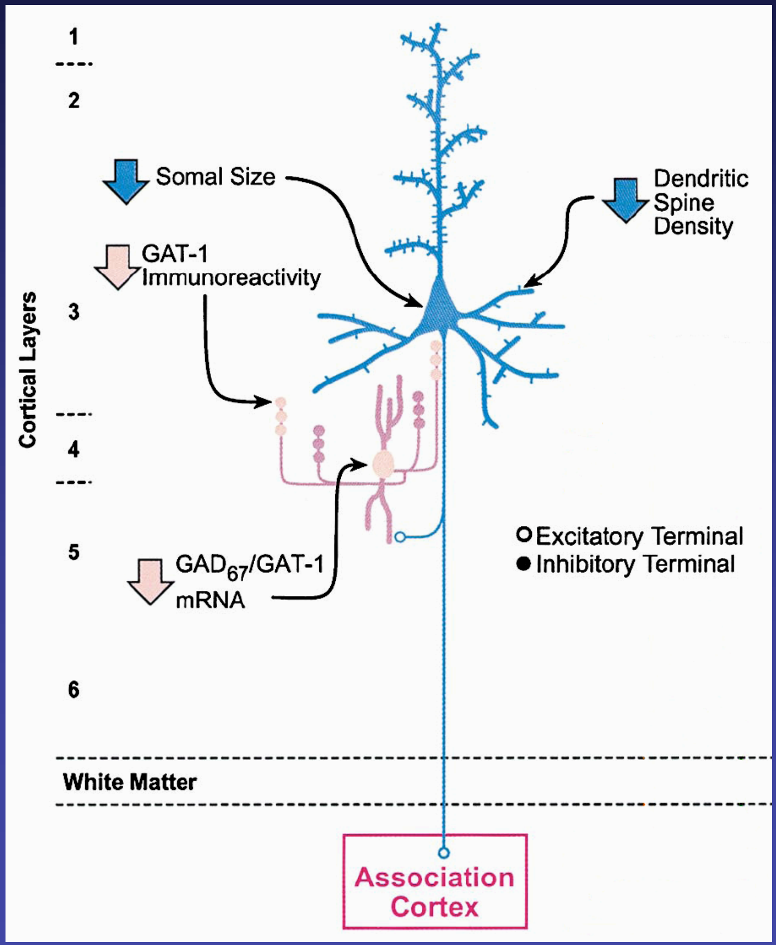


Fries et al. (2007, *Trends Neurosci*)

SZ neural circuitry abnormalities

- Pyramidal cells
  - reduced somal size
  - reduced spine density
  - → reduced synaptic connectivity
- PV+ inhibitory interneurons
  - reduced GABA synthesis, reuptake
- Reduced synaptic connectivity, GABA synthesis can cause γ deficits.
  - Link basic and clinical findings.
  - Suggest targets for translational approaches (e.g., Lewis et al., 2008, *Am J Psychiatry*).

Lewis & Lieberman (2000, *Neuron*)

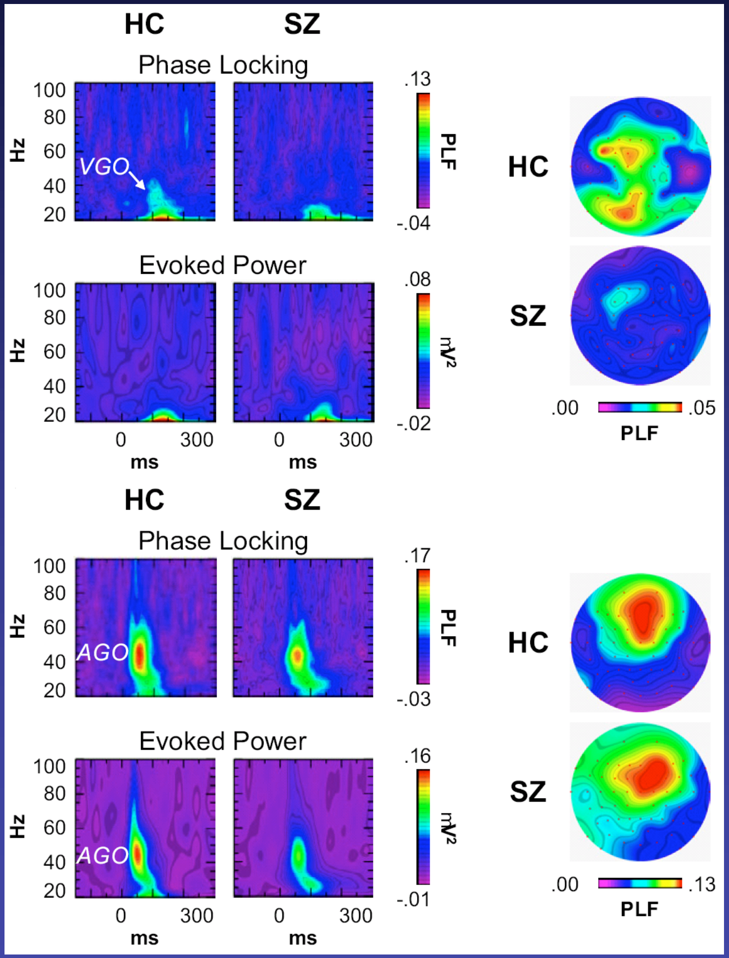


Survey of SZ oscillation studies

- Sensory
  - Evoked and steady-state responses (SSRs)
- Perceptual
  - Gestalt perception
- Cognitive
  - Working memory
- Motor
  - Corollary discharge

Sensory-evoked γ oscillations

- Early auditory-evoked γ
  - ~50 ms, 30-50 Hz
- Early visual-evoked γ
  - ~100 ms, 25-40 Hz
- Easy to obtain from oddball tasks.
- Auditory γ: mixed evidence for deficits
  - 3/6 studies
- Visual γ: 2/2 studies show deficits

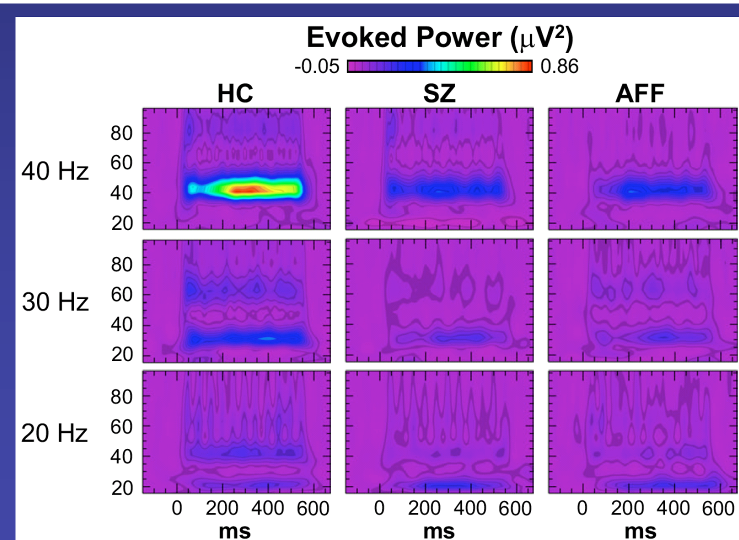


Spencer et al. (2008, *Biol Psychiatry*)

Auditory SSR

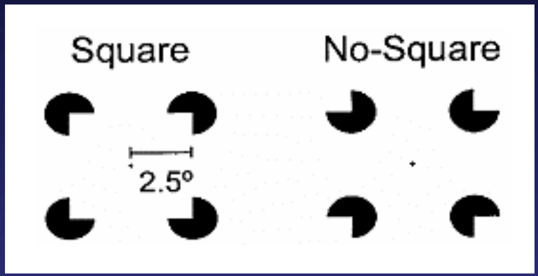
- Passive listening
- 20, 30, 40 Hz click trains
- ASSR reduced in SZ in γ range.
- Deficit found in:
  - Chronic SZ
  - 1st episode SZ
  - Unaffected siblings of SZ
  - Early onset psychosis
  - Bipolar disorder (1st episode & chronic)
    - State dependent (manic, not euthymic)
- Robust deficit, no negative findings reported in ~8 studies.

Kwon et al. (1999, *Arch Gen Psychiatry*)



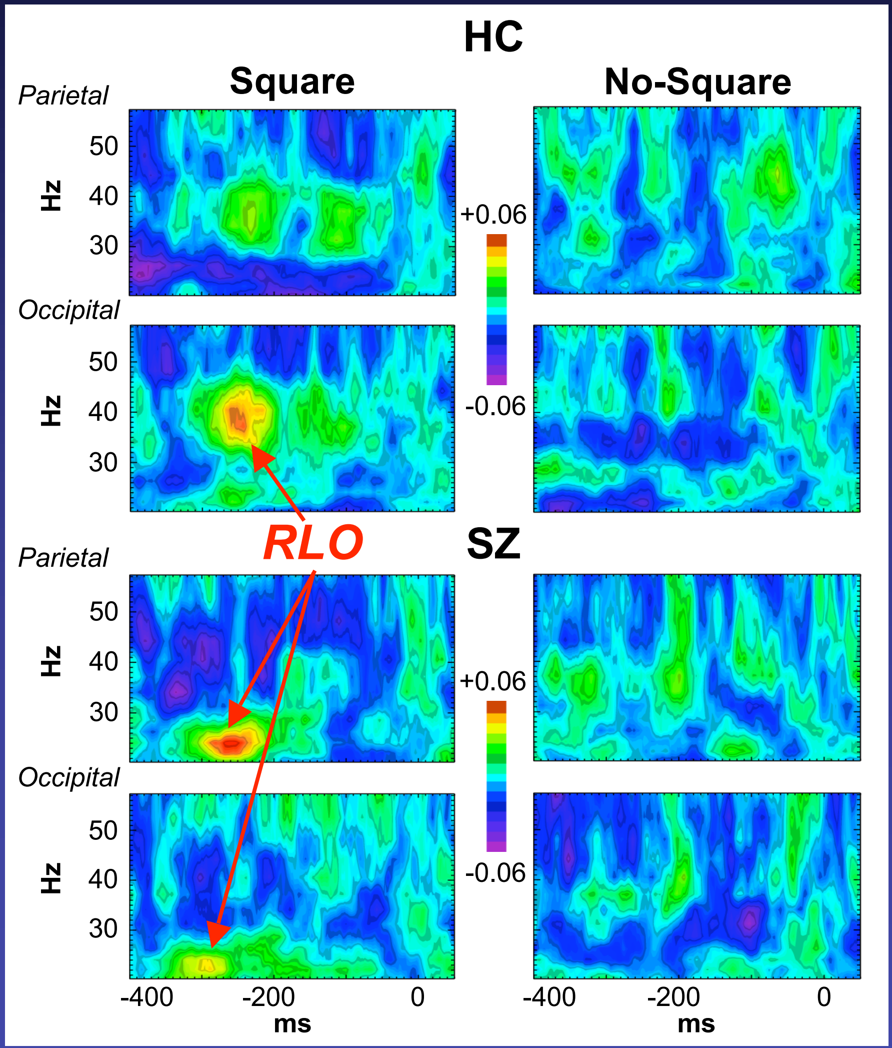
Spencer et al. (2008, *Biol Psychiatry*)

Visual perception studies



- Response-locked γ (RLO) elicited by Gestalt stimuli in controls.
- Frequency shifted to β range in SZ.
- Phase locking *positively* correlated w/ visual hallucinations, disorganization.

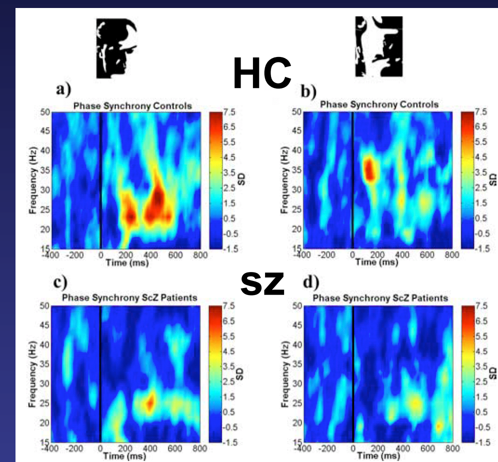
Spencer et al. (2004, *PNAS*)

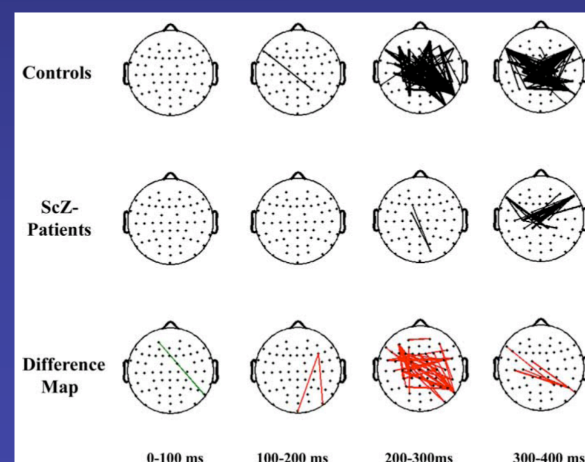


Visual perception studies

- Gestalt stimuli elicited inter-regional β phase synchronization.
- Local γ power did not differ between conditions, subject groups.
- Reduced β inter-regional synchronization in SZ.

Uhlhaas et al. (2006, *J Neurosci*)

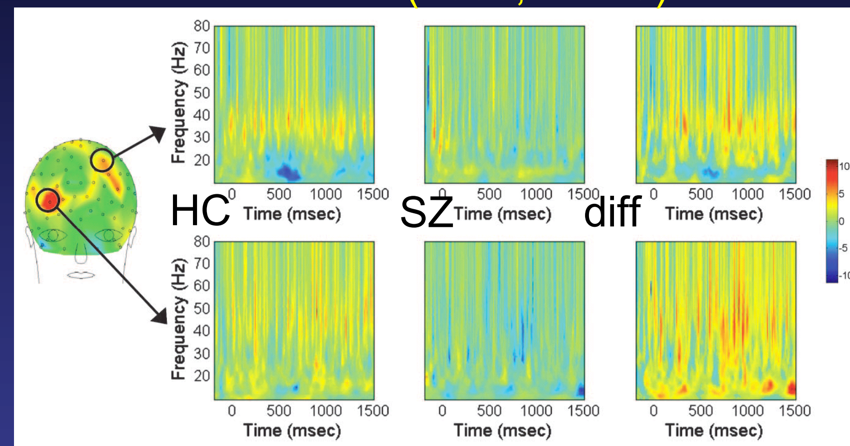




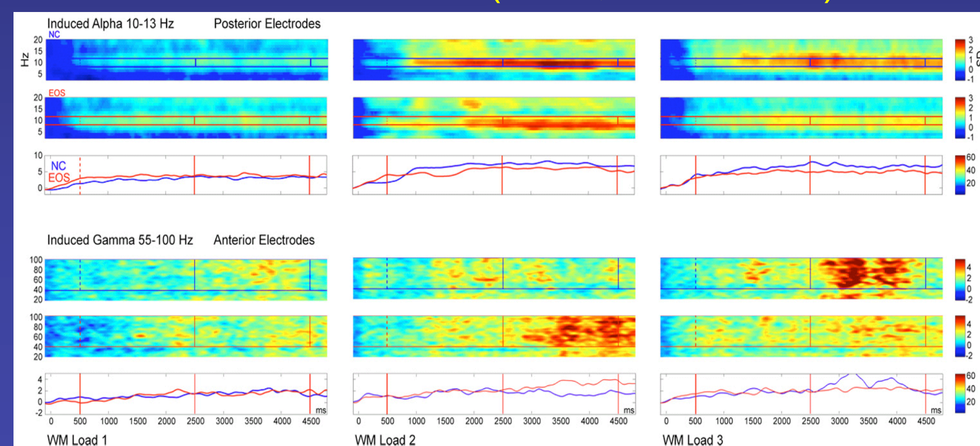
Working memory

- Synaptic connectivity and interneuron abnormalities found in prefrontal regions involved in WM.
- WM processes may involve γ oscillations.
- Delay-period γ deficits in 2/2 studies.
- WM α related to suppression of irrelevant items.
  - No α deficits found.
- Also encoding and retrieval γ deficits.

Cho et al. (2006, *PNAS*)



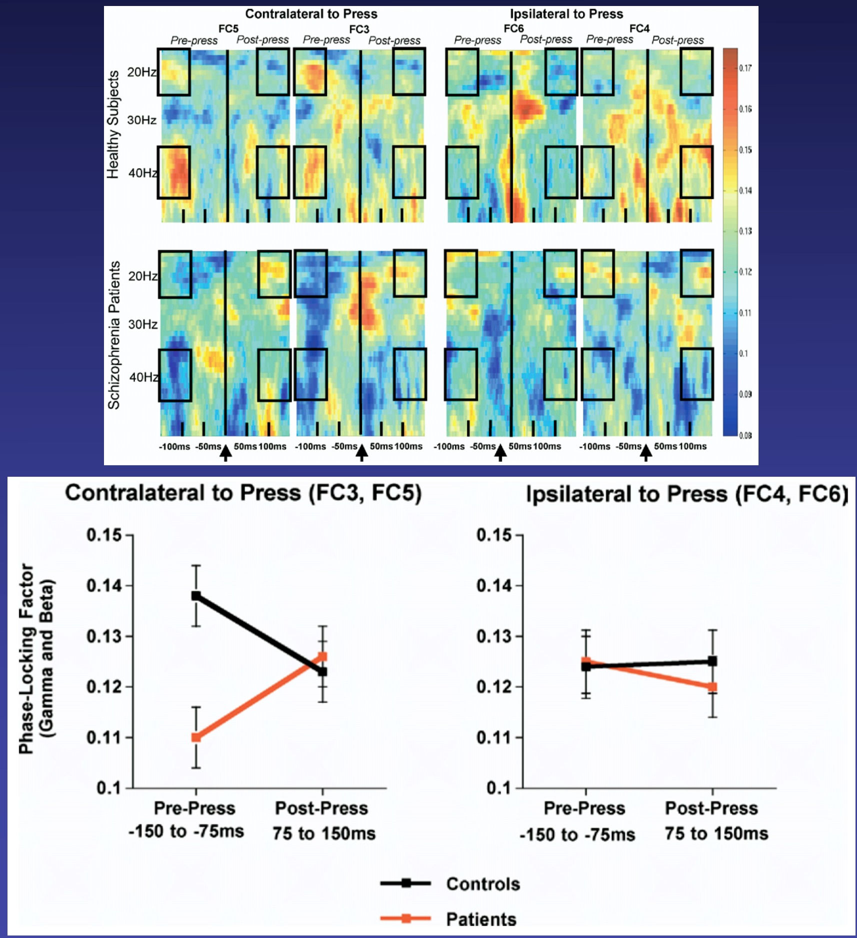
Haenschel et al. (2009, *J Neurosci*)



Motor – corollary discharge

- Self-paced button presses.
- Controls showed a putative corollary discharge-related γ oscillation preceding the button press.
- Pre-press γ was reduced in SZ.
- In SZ, pre-press β was negatively correlated with avolition/apathy ratings.

Ford et al. (2008, *Biol Psychiatry*)



Summary: SZ γ abnormalities

- γ oscillation abnormalities have been found across a variety of domains in SZ.
- Generally power/phase synchronization is reduced in SZ.
  - Consistent with synaptic connectivity, GABA deficits.
- But some positive correlations w/ symptoms have been reported.
  - Consistent with NMDA receptor hypofunction (e.g, Pinault, 2008, *Biol Psychiatry*).

Pharmacological effects

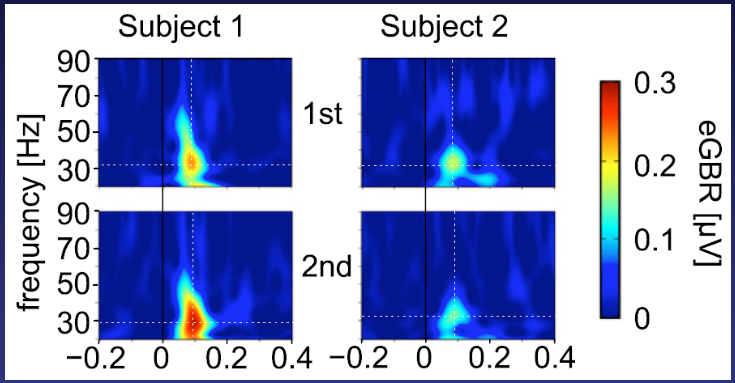
- ASSR in SZ
  - Hong et al. (2004, Schizophr Res)
    - SZ on atypical antipsychotics had larger 40 Hz ASSRs than controls.
    - SZ on conventional antipsychotics had reduced 40 Hz ASSRs.
  - But this medication effect not seen in large sample of Light et al. (2006, *Biol Psychiatry*).
- Early auditory γ in healthy individuals
  - Ahveninen et al. (1999, *Neurosci Lett*)
    - Increased by scopolomine (muscarinic agonist).
    - Consistent with muscarinic & cholinergic enhancement of γ in cat visual cortex (Rodriguez et al., 2004, *J Neurosci*).
  - Jääskeläinen et al. (1999, *Neurosci Lett*)
    - Decreased by benzodiazepine ($GABA_A$ agonist).
  - Jääskeläinen et al. (2000, *Psychopharmacol*)
    - Decreased by ethanol ($GABA_A$ agonist).
- ASSR and cannabis use
  - Skosnik et al. (2006, Am J Psychiatry)
    - Cannabis users vs. naïve subjects had decreased 20 Hz ASSR (& 40 Hz harmonic), but normal 40 Hz ASSR.

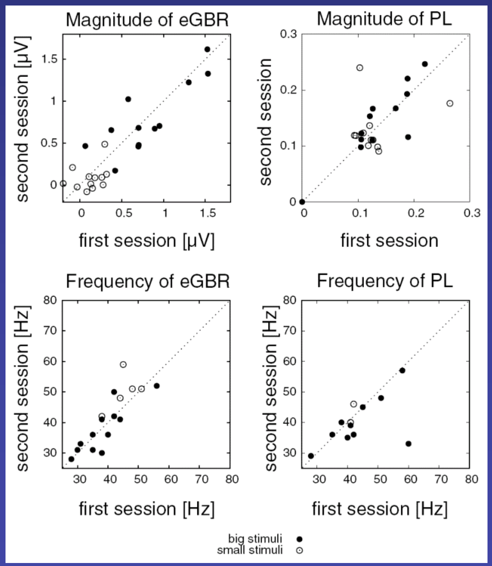
Overview

- What is time/frequency (T/F) analysis?
- What can T/F analysis tell us about schizophrenia?
- Issues in utilizing T/F analyses
  - Test/re-test reliability
  - Planning experiment
  - Acquiring, analyzing data
  - Functional connectivity confounds
- Questions and future directions

Test/re-test reliability

- Very little data to date.
- Frund et al. (2007, Clin Neurophysiol)
  - 12 young, healthy subjects.
  - 2 week interval.
  - Early visual γ oscillation.
  - High reliability:
    - Magnitude & peak frequency for evoked power and phase locking > 0.78.





Planning the experiment

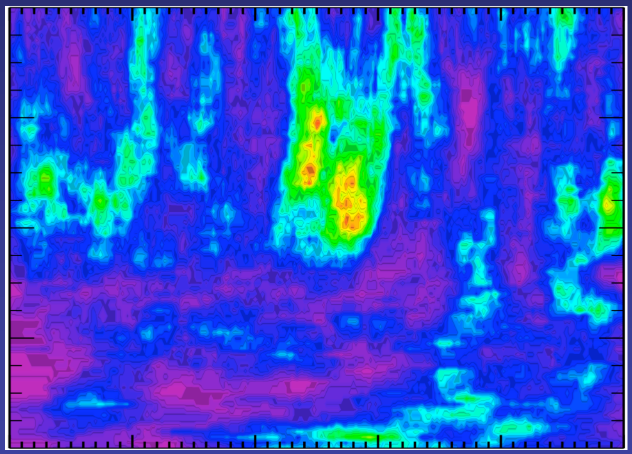
- Have adequate # trials for good signal-to-noise ratio (SNR).
  - > 60 per condition (?), the more the better.
  - Coherence values may be overestimated for small trial #s.
- Equal numbers of trials per condition to match SNR (if possible).
- Epoch length should take into account frequency range of interest.
  - Baseline and post-stimulus periods should each be at least 1 cycle duration of the lowest frequency.
  - Just because your software gives you low frequencies doesn't mean they're valid.

Acquiring the data

- Very important to acquire clean data
  - More important than for ERPs – can't filter out noise.
- Avoid line noise, monitor refresh artifact.
- Have subjects relax to reduce muscle artifact.
- Set amplifier filter to widest reasonable range (e.g, DC to 100 Hz or higher).
- Sample at fast rate
  - Nyquist frequency: highest measurable frequency is ½ the sampling rate.
  - But phase resolution better with higher sampling rate.
- Monitor eye movements for microsaccades?

Analyzing the data

- Choose frequency resolution suitable for your purposes.
  - Analysis of frequency variability requires high resolution (1 Hz steps).
- Baseline correction?
  - 0 has real meaning for power, phase locking.
  - But necessary for examining true event-related effects.
  - Subtraction, percentage, Z-score?
- Parametric vs. nonparametric statistics?
  - Phase locking values probably not normally distributed (0-1).
  - Parametrics may be OK in practice.
- Statistical mapping
  - How to correct for multiple comparisons in T/F space?
  - Resampling methods (bootstrapping, permutation)



Functional connectivity confounds

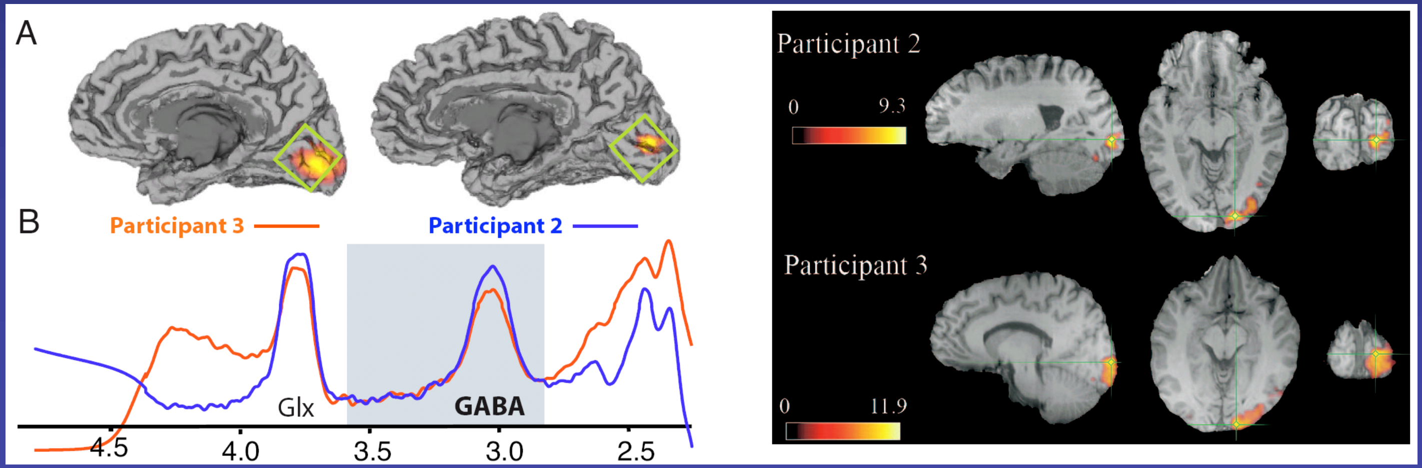
- Volume conduction
  - Potentials propagate throughout head.
  - Can lead to false synchronization.
- Common reference
  - Synchronization effects may be due to changes at the reference electrode(s).
  - No such thing as an inactive site.
- Nunez, Guevara et al. (2004, *Neuroinformatics*), Sazonov et al. (2009, *Biol Cybern*), others
- Solutions
  - Statistical correction?
  - Current density, MEG: reference-free, attenuate volume conduction.
  - Source modeling: ideal, but difficult at present.

Where do we go from here?

- To be useful as biomarkers, SZ oscillation abnormalities should be correlated with symptoms and/or cognitive deficits.
- Understanding the underlying causes of particular abnormalities would enhance their utility as biomarkers.
  - Animal and computational models of particular oscillations need to be developed.

Future directions

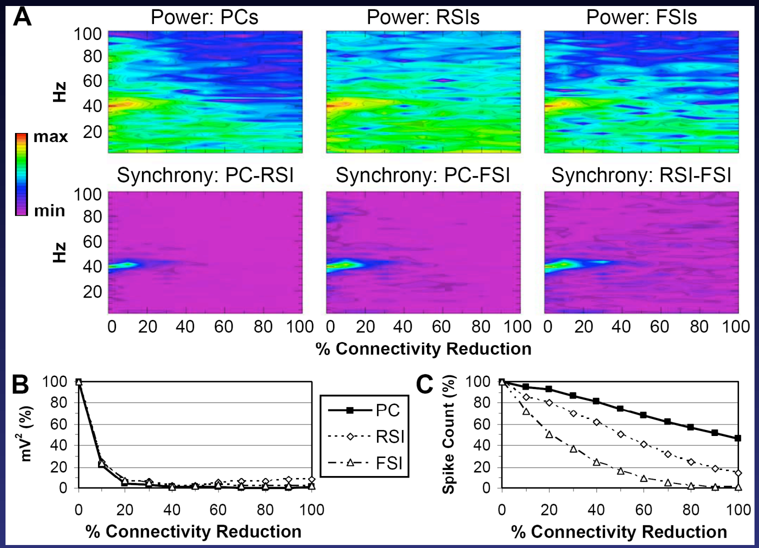
- Need to map oscillation (and ERP) abnormalities onto anatomy.
  - How do anatomical and physiological deficits correlate?
- Integrate multiple methodologies to assess neural circuit integrity.
  - Source localized EEG/MEG, fMRI, TMS, MRS, and MRI/DTI measures of anatomy.



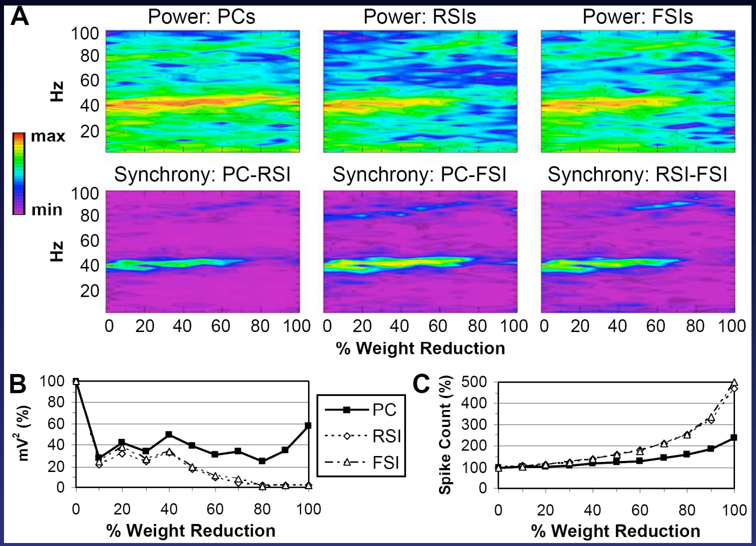
Muthukumaraswamy et al. (2009, *PNAS*)

Thanks for your attention.

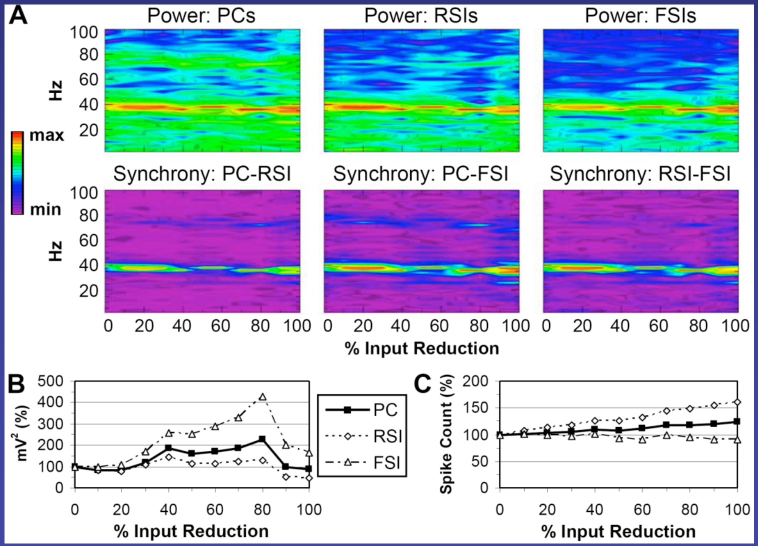
Synaptic Connectivity



Interneuron GABA Output



Interneuron NMDA Input



Spencer (2009, *Front Hum Neurosci*)