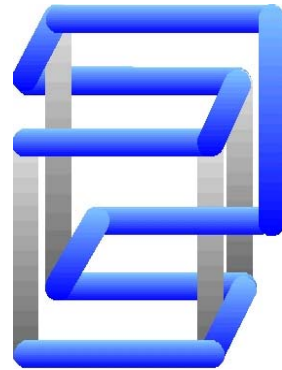


# Statistical assessment of linear and nonlinear causal interactions



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## Introduction

This study is part of an effort to develop a framework for inferring space-time causal interactions via whole-brain modalities such as M/EEG and fMRI. An information theoretic approach for treating linear and general nonlinear time-lagged interactions (such as those between brain regions, mediated by white matter) was introduced at last year's meeting [4]. Statistical assessments may be made in the context of an

event-related experiment via nonparametric permutation tests [6]. Under “resting” or “baseline” conditions, however, there are no experimental labels that can be permuted (or otherwise randomized). Following the pioneering study of Biswal et al. [1], the functional connectivity of such “resting state networks” has been a topic of growing interest. Thus, the specific aim of this study is to develop a statistical test for baseline causality measures. The approach is to generate *surrogate data* that studiously reconstructs all statistical properties of the baseline dataset of interest while (at the same time) the causal relationship of interest is studiously omitted.

## Theory

A brain region  $A$  process has a causal effect on a brain region  $B$  process at time lag  $s$  if the state of  $A$  at time  $t$ ,  $A(t)$ , contains predictive information about the subsequent state of  $B$ ,  $B(t+s)$ , while neglecting contributions from “noncausal confounds” such as  $B(t)$ ,  $A(t+s)$ , or the states of another brain region  $C$  that may drive or mediate apparent interactions between  $A$  and  $B$ . Note that states generally are vectors, and that “causality” in this framework is an asymptotic ideal that could be achieved only by including all noncausal confounds.

Purely predictive information is the simple mutual information quantity  $I(A(t), B(t+s))$ , whereas causal information is the *conditional mutual information* quantity  $I(A(t), B(t+s) |$

$A(t+s)$ ,  $B(t)$ ,  $C_1(t_1)$ , ...,  $C_n(t_n)$ ). These may be computed via multivariate differential entropies [4], which (by contrast with discrete entropies) have no absolute zero; they are relative to the state vector coordinate systems. *Linear* entropy relative to original state coordinates equals the entropy change after a sphering linear transformation has removed all Gaussian content from the joint state distribution. *Nonlinear* entropy is computed relative to the transformed states, and thus depends only on residual non-Gaussian properties.

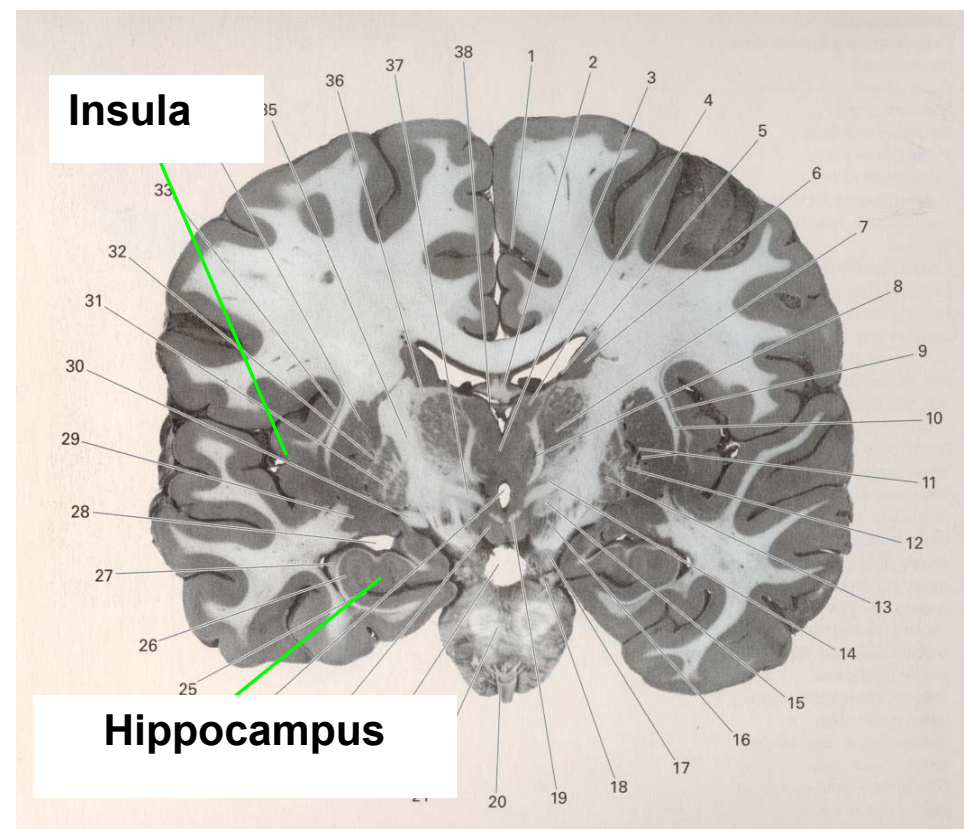
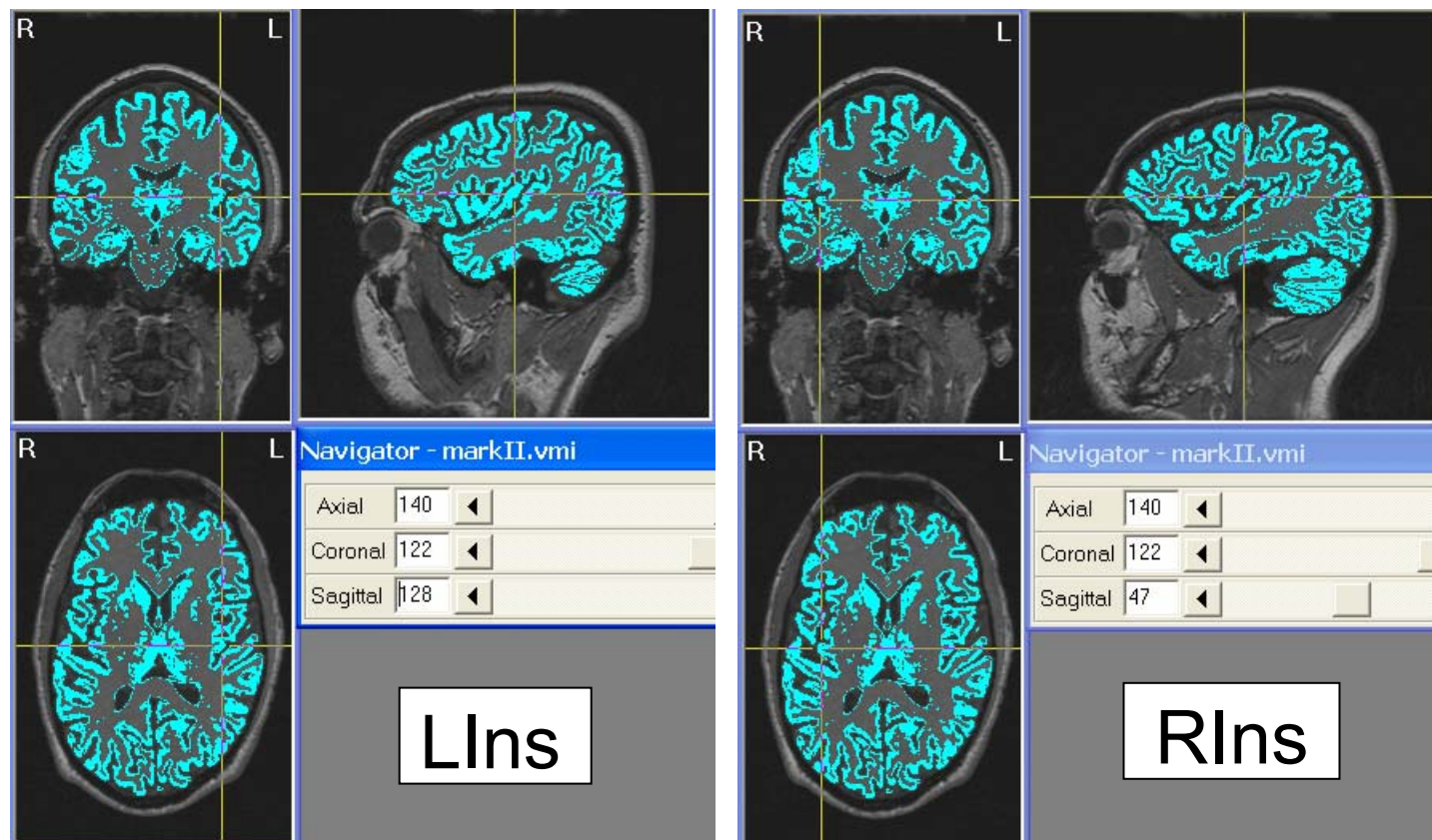
Four measures of inter-regional brain interactions in this framework are: *linear predictive mutual information* (IPMI), *nonlinear predictive mutual information* (nPMI), *linear causally conditional mutual information* (ICCMI), and *nonlinear causally conditional mutual information* (nCCMI). Because IPMI and nPMI are based on mutual information—a general measure of non-independence—a simple statistical test for these may be constructed by operating directly on the state data to destroy all joint timing relationships between  $A(t)$  and  $B(t+s)$ . By contrast, special surrogate data generation is required to construct randomization tests for ICCMI and nCCMI because it is required to selectively destroy only those relationships between  $A(t)$  and  $B(t+s)$  that are unmediated by the noncausal conditions (i.e., mediated relationships must be preserved).

A general procedure for doing this is as follows: (i) generate a random non-causal confound vector from its marginal probability density; (ii) generate a random state

vector  $A(t)$  conditional on the non-causal vector generated in the first step; and (iii) independently generate a random state vector  $B(t+s)$  conditional on the same non-causal vector. Thus,  $A(t)$  and  $B(t+s)$  may be related in this process, but *only through the non-causal conditions*. The surrogate data generated by this procedure has the statistical properties of the actual data, except that any direct relationship between  $A(t)$  and  $B(t+s)$  has been destroyed. The distributions of ICCMI or nCCMI for the surrogate data are the *null* distributions that may be used to obtain p-values. In the case of ICCMI, the full multivariate joint state distribution is Gaussian, from which it follows that the marginal distribution of (i) and the conditional distributions of (ii) and (iii) are also Gaussian, with known forms that depend only on covariances (assuming zero means).

## Methods

The general statistical approach is illustrated for the linear case using a resting state EEG dataset. A 39 s sample of clean (ocular corrected) 256-channel EEG was subsampled to the 128 odd-numbered channels. From the subject's own MRI, a boundary element head model was constructed, and a gray matter source space model obtained. Regions of interest were specified; then regional activity estimators were derived based on brain-head-electrode geometry [5]. Complex demodulation [3] was used to obtain regional state space vectors; then ICCMI was computed per lag.



RIns	Right Insula
LIns	Left Insula
RHipp	Right Hippocampus
LHipp	Left Hippocampus

Figure 1. Insula and Hippocampus located on a coronal section through mamillary bodies. From reference [2], p. 64.

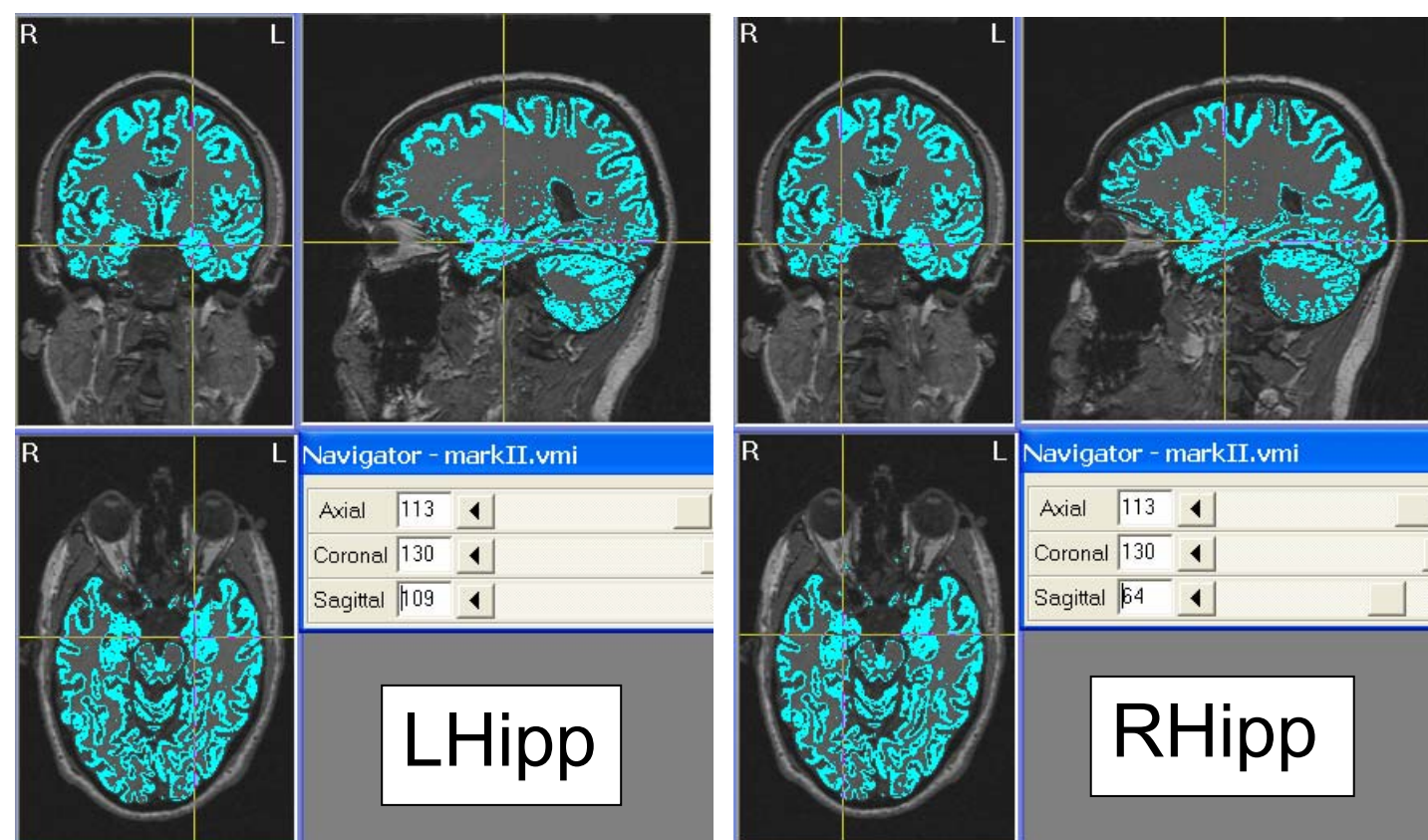


Figure 2. Centers of four regions of interest, {right, left} x {insula, hippocampus}, shown in axial, coronal, and sagittal views. Blue identifies gray matter region used for REGAE source space model.

**Regional activity estimation (REGAE)** is a method for estimating brain activity in regions of interest (ROIs) from EEG or MEG data [5]. It is a local estimator (3D spatial filter) that discriminates activity emitted from the ROI from activity that could be emitted simultaneously from the remainder of the source space (typically, all gray matter). In this study, ROIs were centered as shown in figure 2, and were expanded in gray matter just enough to achieve a criterion of AUROC = 0.75. Gaussian standard deviations ranged from 17.5 to 24.2 mm. All ROIs had estimator dimension = 6, which was reduced to 1 or 2 after applying SVD to the estimated data time series. See figure 3a below.

**Complex demodulation** is a technique for deriving a complex-valued time series that represents oscillatory activity centered on a given frequency  $f$ , with a given symmetric bandwidth [3]. The modulus of the complex value at time  $t$  is the envelope of the oscillatory activity. The rate at which the envelope can change is limited by the bandwidth around the center frequency (i.e., as the bandwidth narrows, so does the rate at which the envelope can change). In this study—based very roughly on frequencies observed in figure 3b below—the following four frequency bands were utilized:  $4.4 \text{ Hz} \pm 1.6 \text{ Hz}$ ,  $7.5 \text{ Hz} \pm 2.5 \text{ Hz}$ ,  $12.5 \text{ Hz} \pm 3.5 \text{ Hz}$ , and  $21.5 \text{ Hz} \pm 6.5 \text{ Hz}$ . Figure 3c below illustrates the result of applying complex demodulation to the REGAE-derived time series.

Figure 3a: REGAE-derived, reduced time series (1 s displayed)

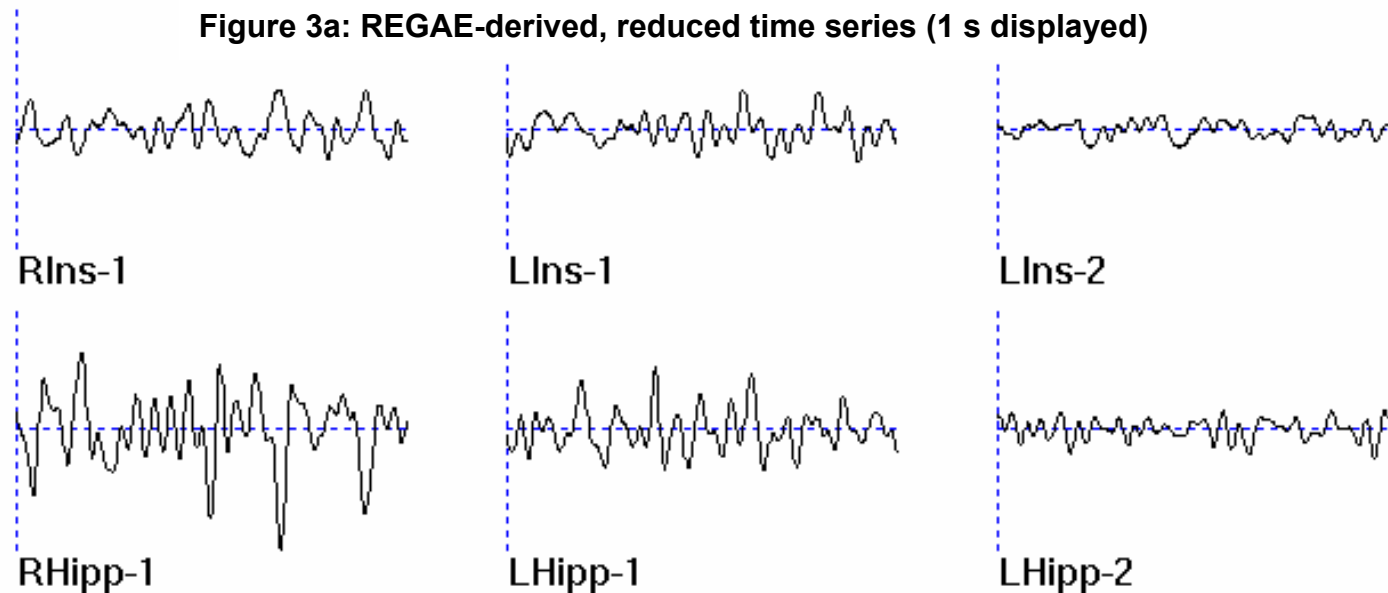


Figure 3b: Spectra from 10s of data (0-30 Hz, 4.8 Hz marked)

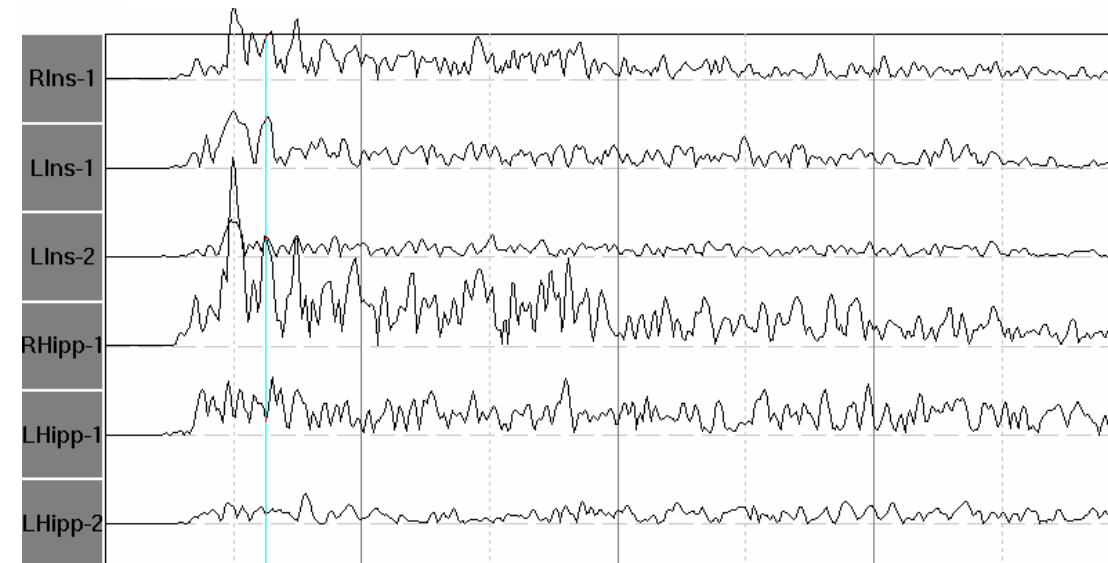
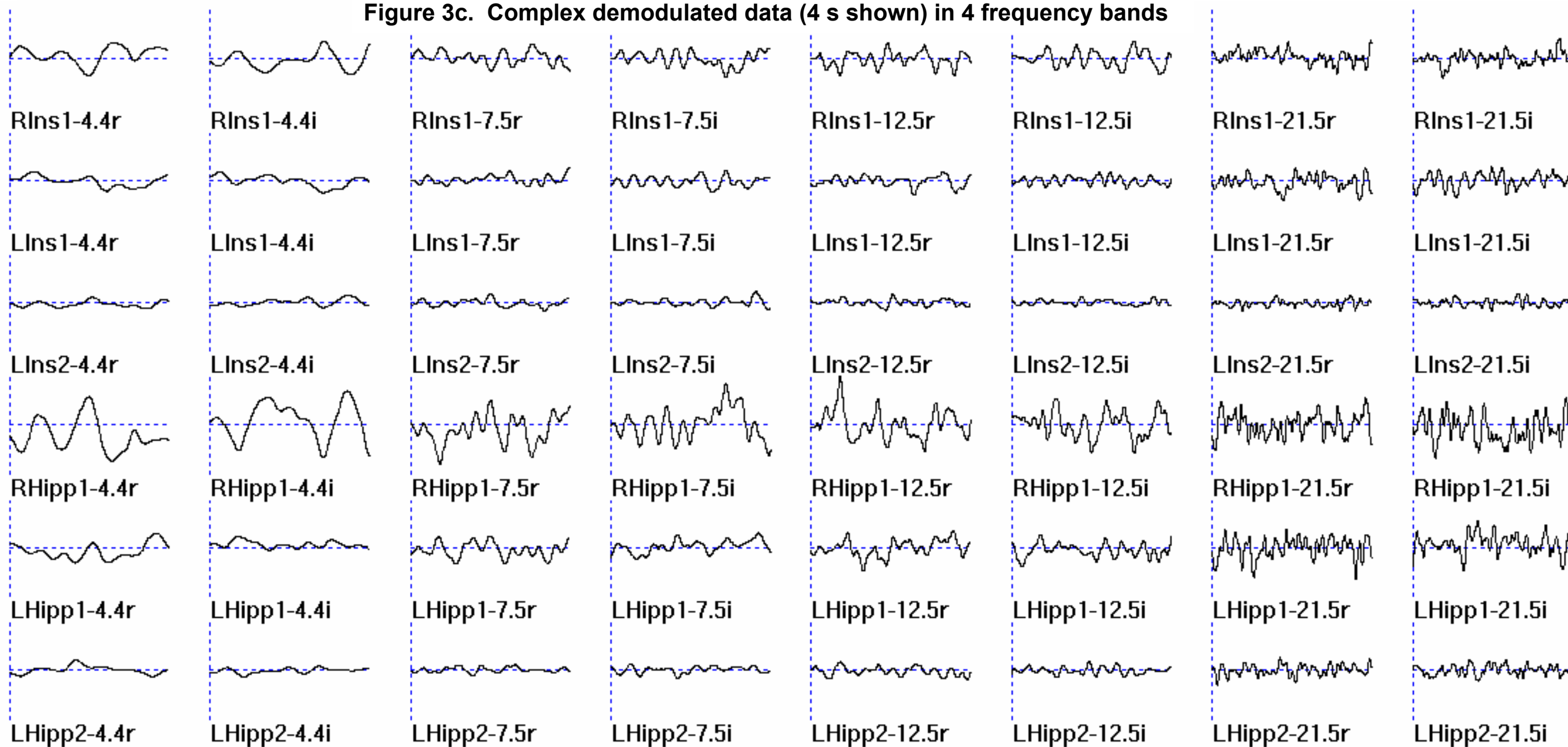
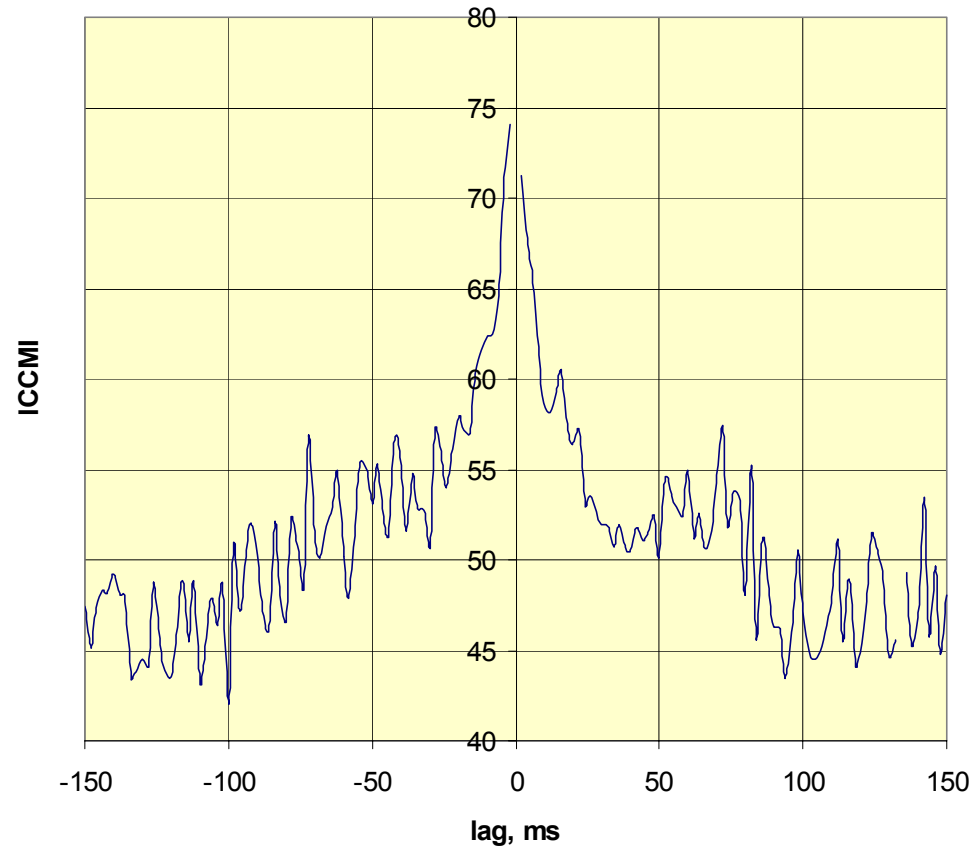


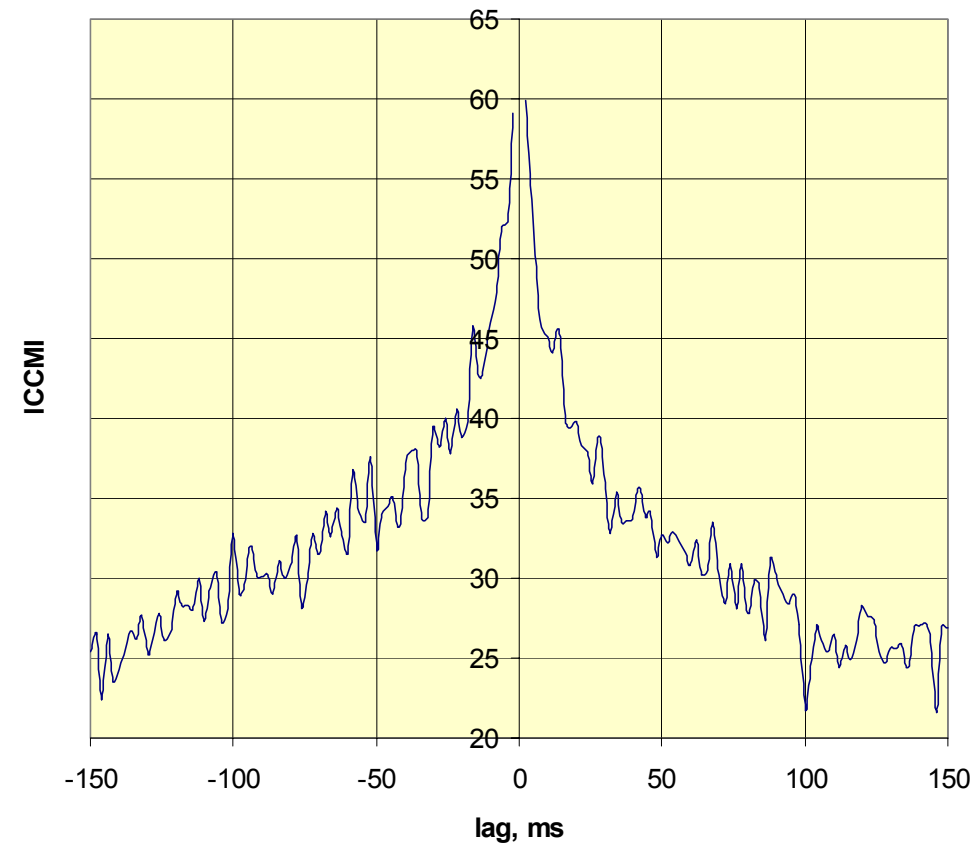
Figure 3c. Complex demodulated data (4 s shown) in 4 frequency bands



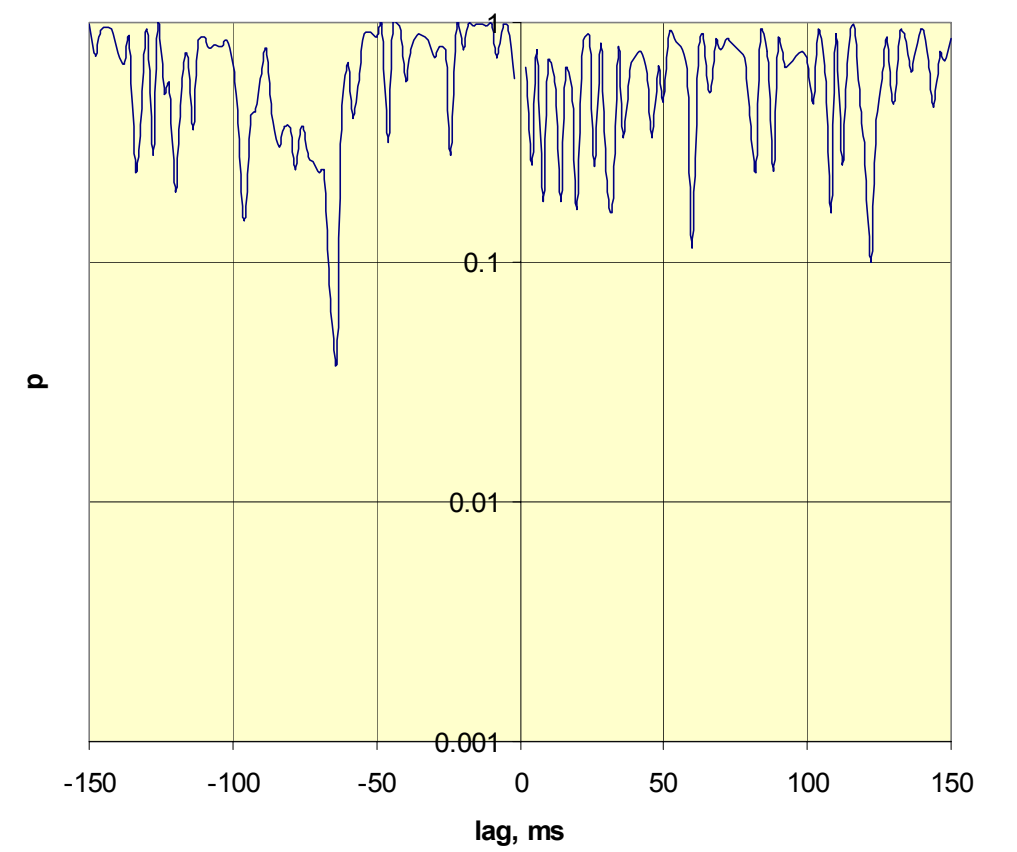
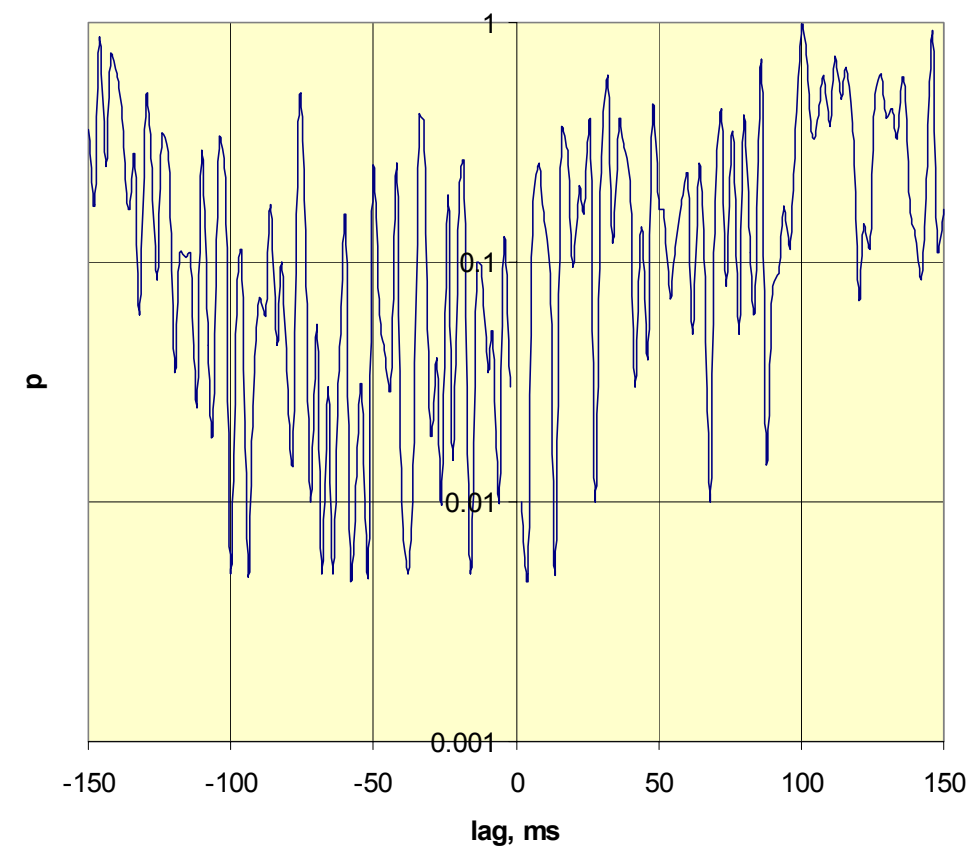
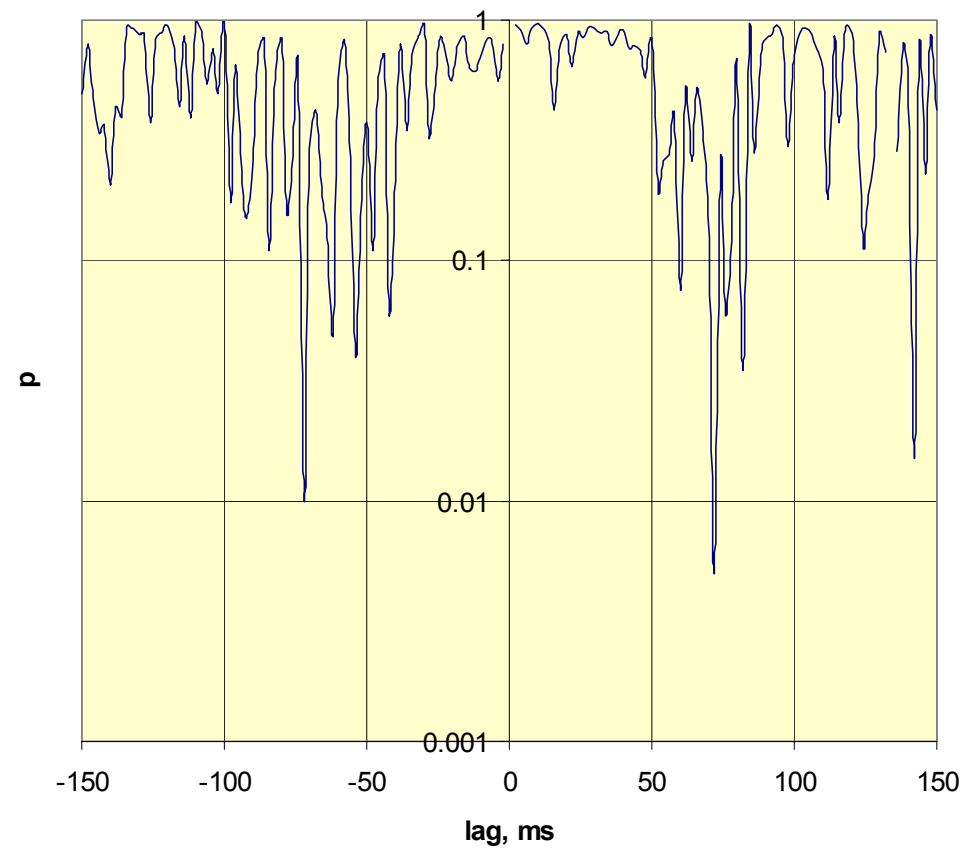
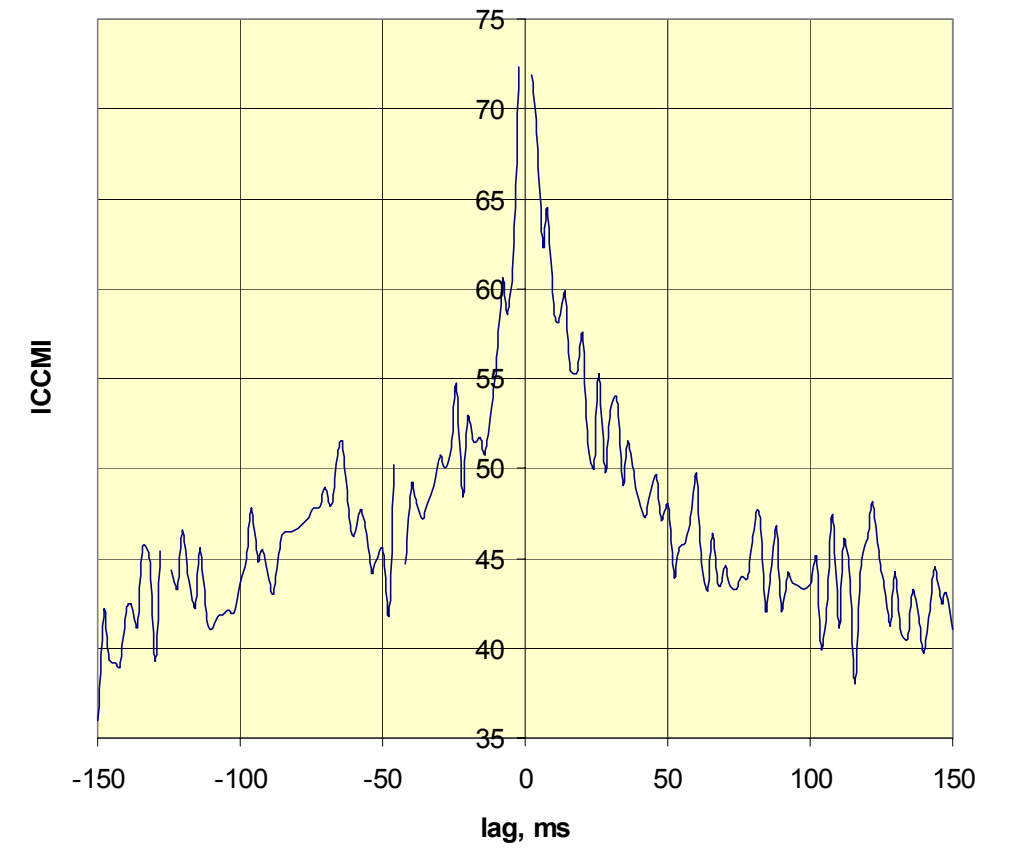
### RIns::LIns



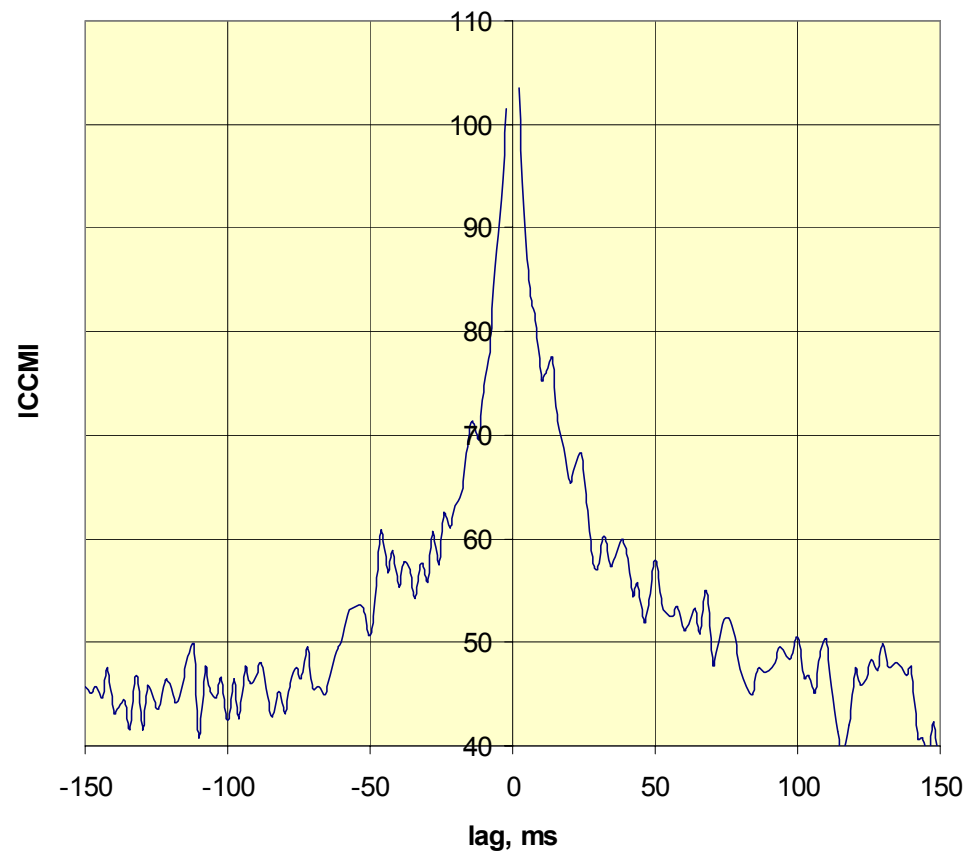
### RIns::RHipp



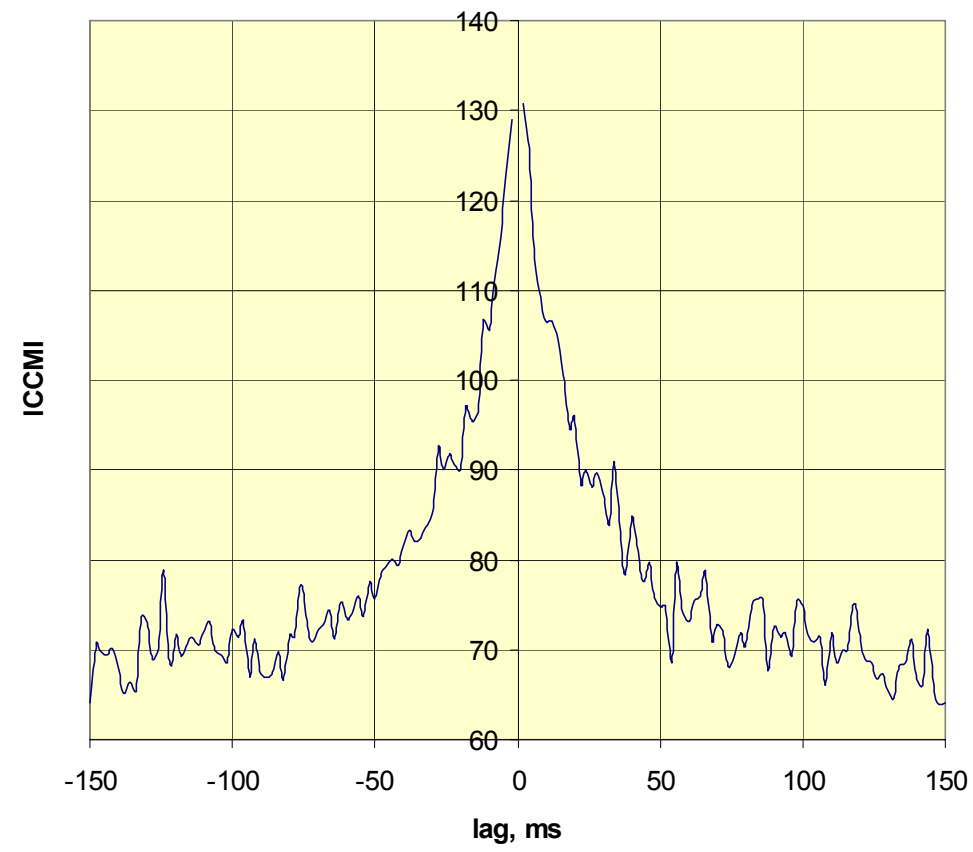
### RIns::LHipp



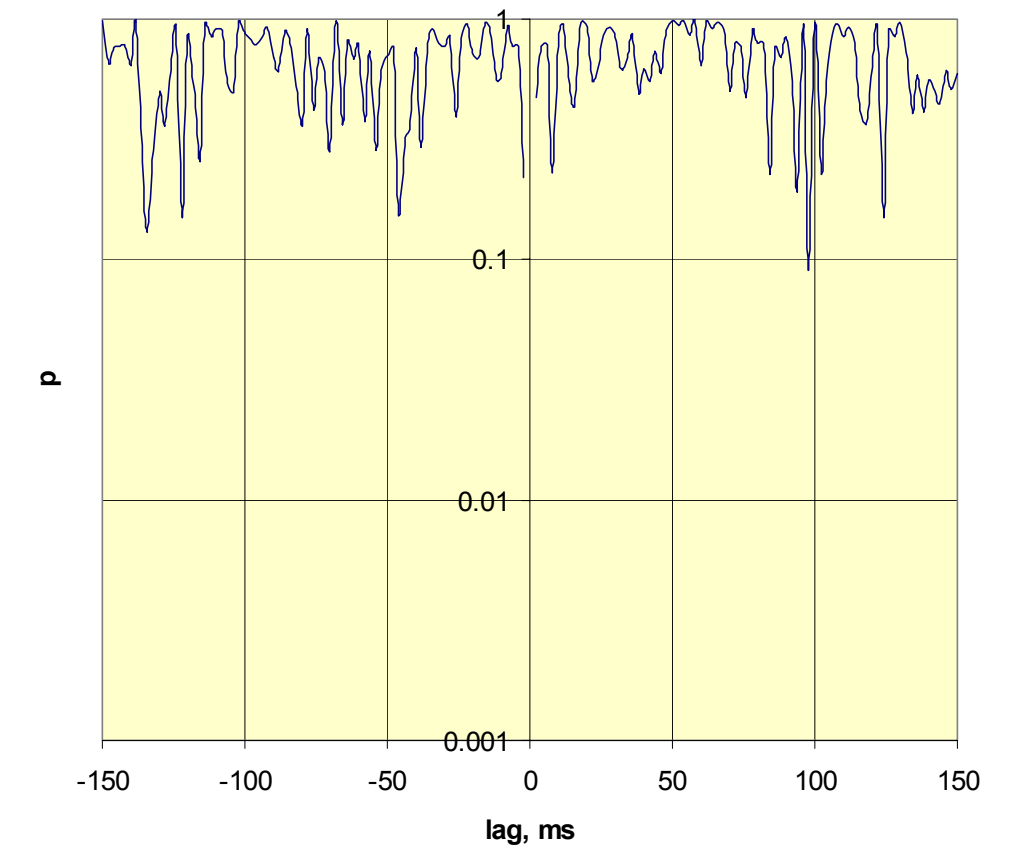
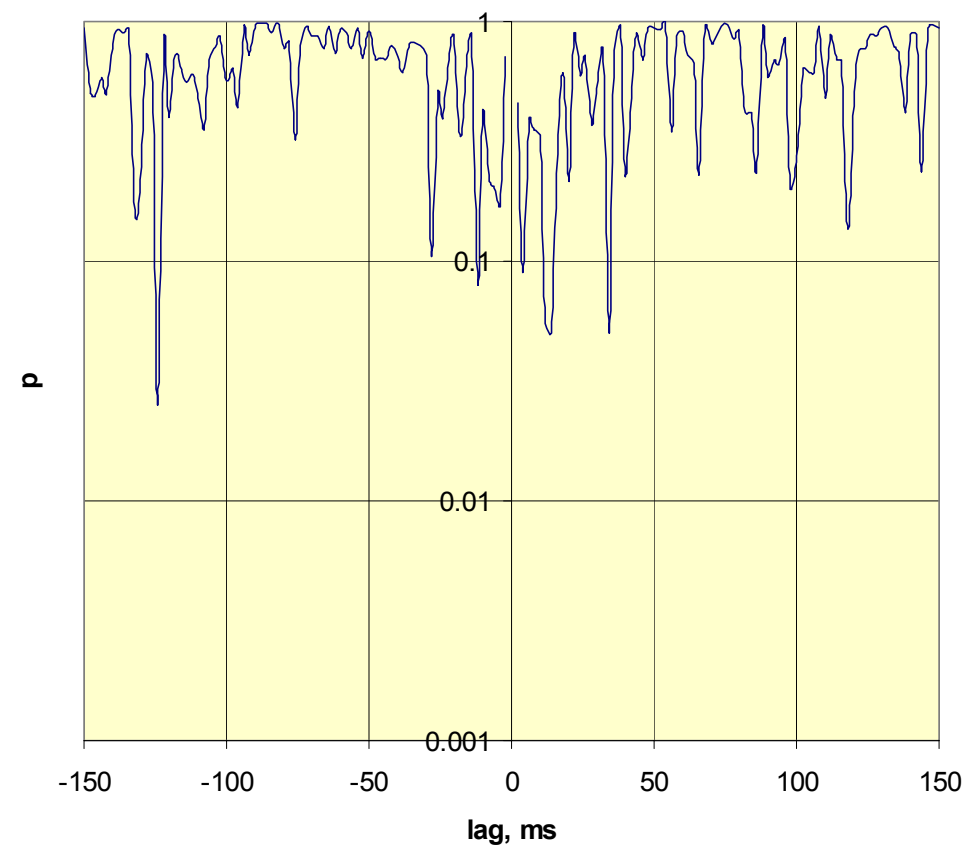
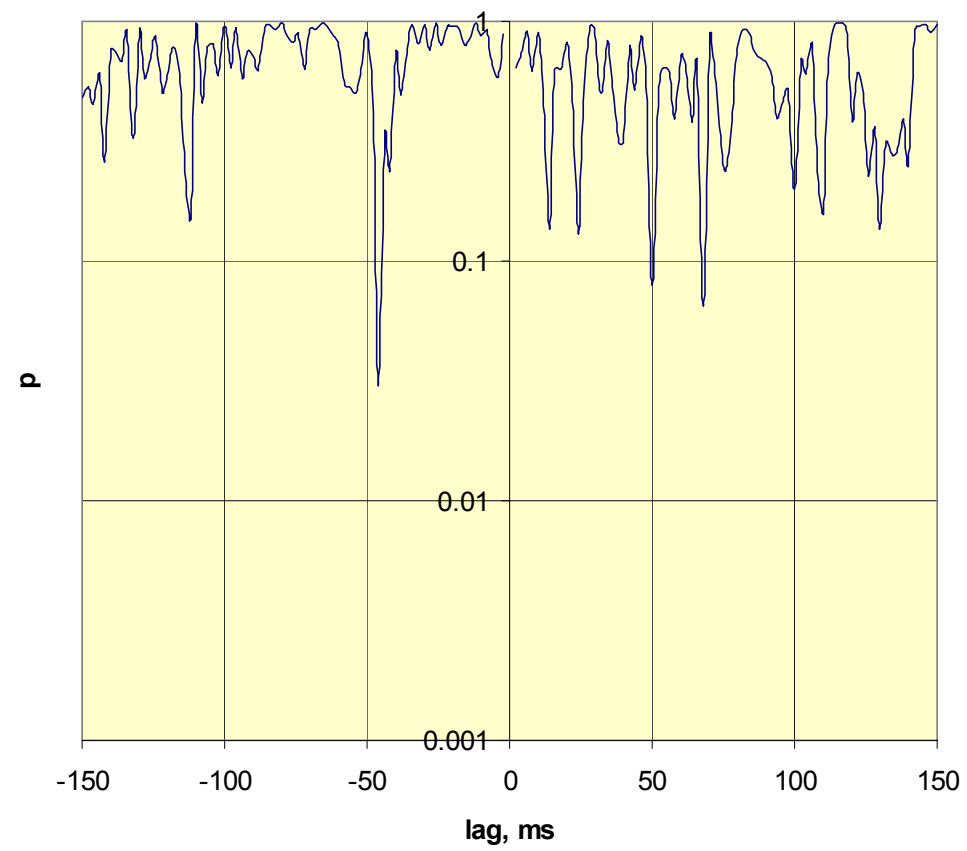
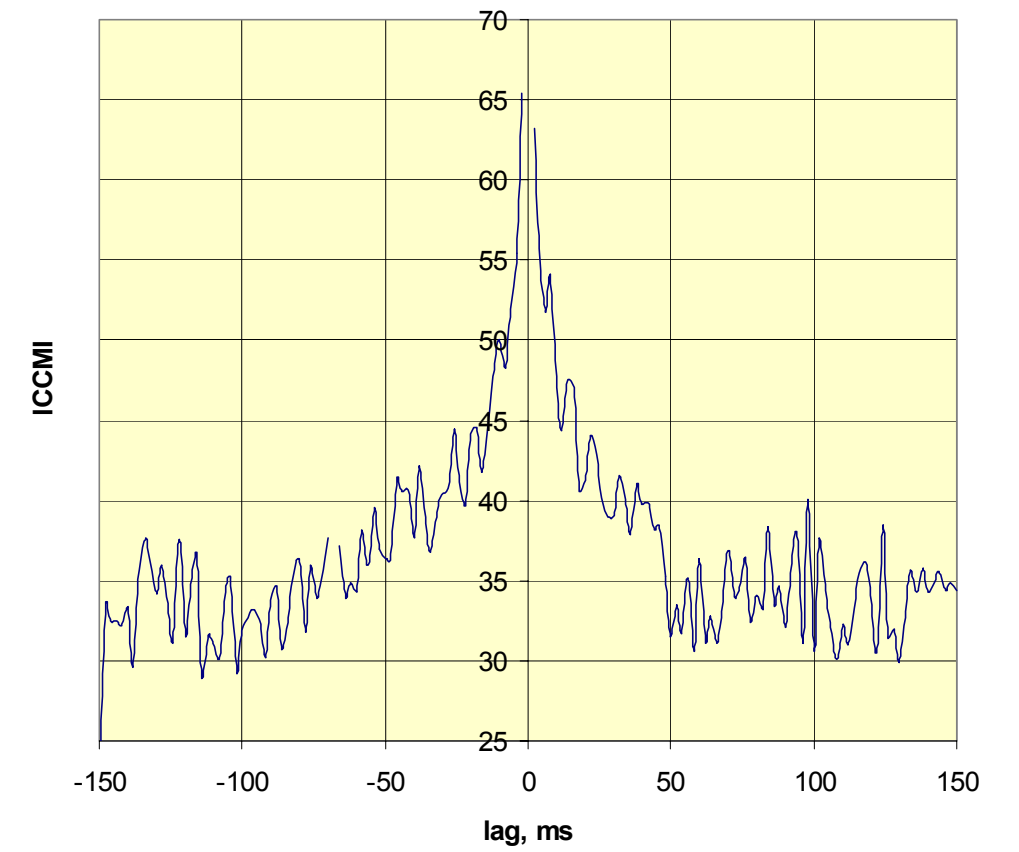
### LIns::RHipp



### LIns::LHipp



### RHipp::LHipp



# Results

Shown above are the results for all 6 ROI pairings. The top rows show ICCMI as a function of inter-ROI lag from  $-150$  ms to  $+150$  ms (where a negative lag means that the first ROI leads the second ROI). All plots have apparent asymptotic peaks at lag zero (where ICCMI is undefined), and are roughly symmetric, however, with numerous asymmetries in detail. By construction of the ICCMI measure, there is assurance that the increasing values near lag zero are not due to instantaneous volume conduction or estimator crosstalk. The bottom rows logarithmically plot the p-values obtained by ranking the results of the corresponding top rows against multiple realizations of the lag-specific surrogate data processes. Evidently, there is no direct correspondence between ICCMI magnitude and p-values. For example, the RIns::LIns local ICCMI peaks at  $\pm 72$  ms are highly significant; but nothing approaches significance at the global maximum near lag zero. Thus, the statistical analysis indicates that there may be rather strong and specific reciprocal functional interhemispheric insular connectivity (although, of course, it remains to rule out mediation or modulation via other brain regions). There are significant interactions between ipsilateral insula and hippocampal regions, which is much stronger on the right than on the left. Insula lead contralateral hippocampi at roughly 50-60 ms. On the other hand, there appears to be little or no direct interaction between right and left hippocampal regions.

# Discussion

Causal inference based on specially constructed conditional mutual information measures, with corresponding surrogate data constructions, is a very general analysis framework. In principle, it may apply to any simultaneously acquired brain imaging time series data. Here it has been applied to resting state EEG data, via regional activity estimation (REGAE) and complex demodulation, with intriguing results. Although computationally more demanding, the principles discussed here are applicable as well to nonlinear causally conditional mutual information measures.

## References

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