Causal inference with multivariate neurophysiological data: Some computational issues

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Source Signal Imaging, Inc.
http://www.sourcesignal.com

Computational Science Research Center
Colloquium 4 December 2009

Collaborators

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  - Péter Érdi (Kalamazoo College; KFKI Budapest)
    - Zsófi Huhn (KFKI Budapest)
- Leo Towle et al. (U Chicago)
- Richard Burgess (Cleveland Clinic Foundation)
  - Rei Enatsu (CCF; Kyoto U)
- Richard Clark & Kath Moores (Flinders)

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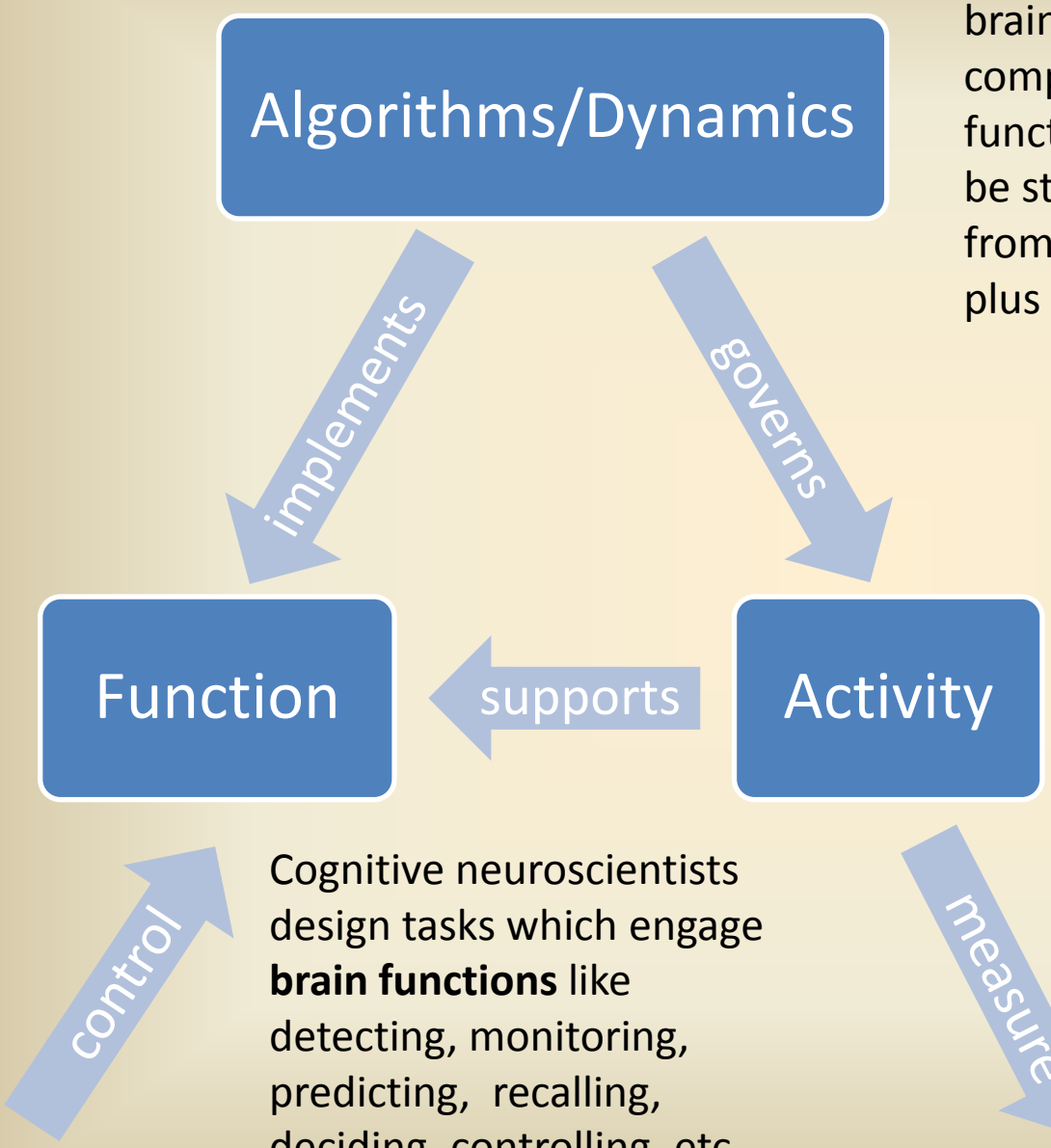
- Bassam Assaf
- Greg Simpson
- Tony Norcia et al. (Smith-Kettlewell)
- Rikki Matsumoto (Kyoto U)
- Jose Castillo

Support

- NIH-NIBIB
- NIH-NINDS
- Source Signal Imaging



Brain dynamics physically govern brain activity, while **brain algorithms** computationally implement brain functions. Algorithms/dynamics must be studied indirectly, i.e., inferred from experimental data plus theory plus modeling.

Conjecture: Brain algorithms are dynamic, and brain dynamics are algorithmic. I.e., physics and computation are deeply united in the brain at all organizational levels.

Cognitive neuroscientists design tasks which engage **brain functions** like detecting, monitoring, predicting, recalling, deciding, controlling, etc.

Neuroimaging and neurophysiological measures reflect **brain activity**, e.g., hemodynamic (~energy) or neuroelectric (~information)

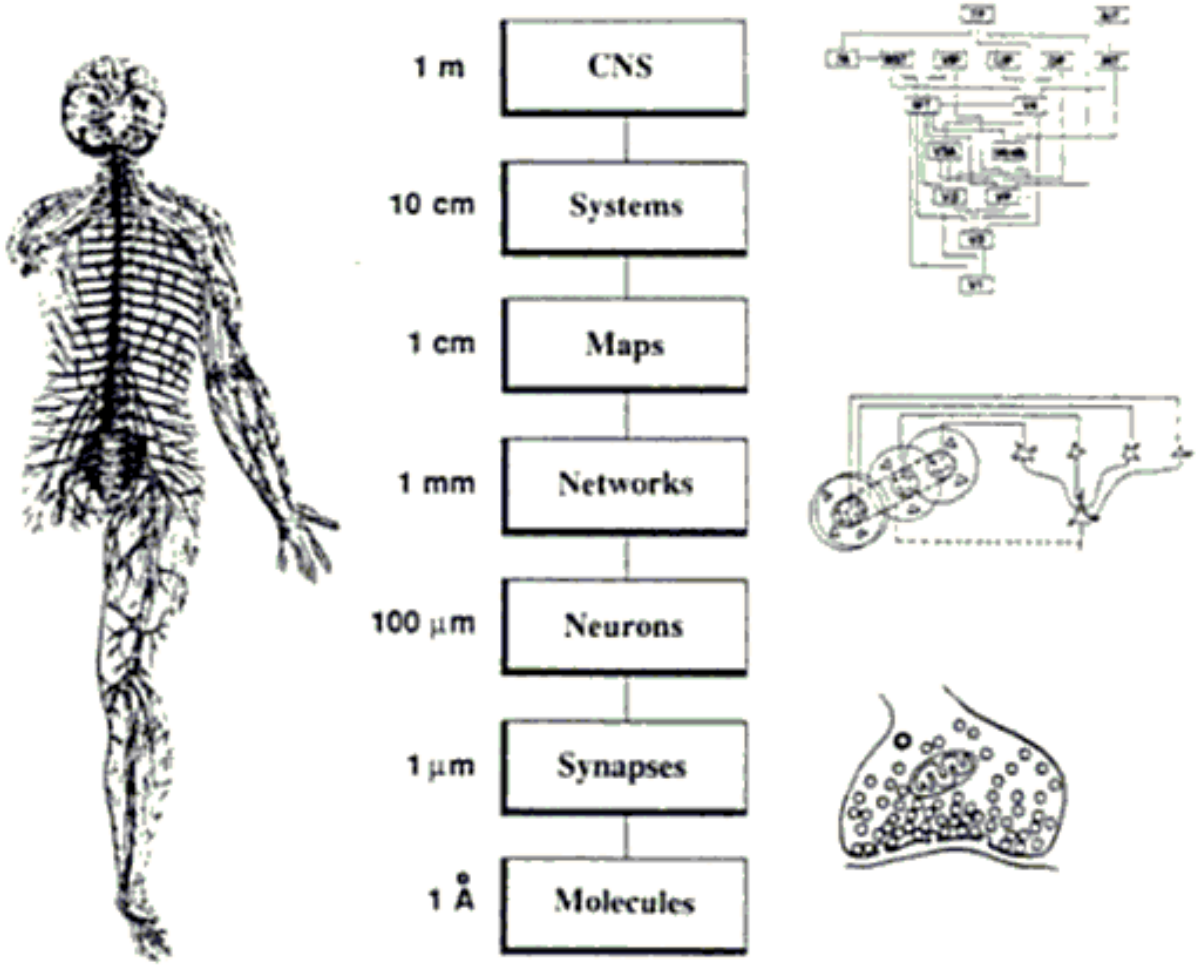


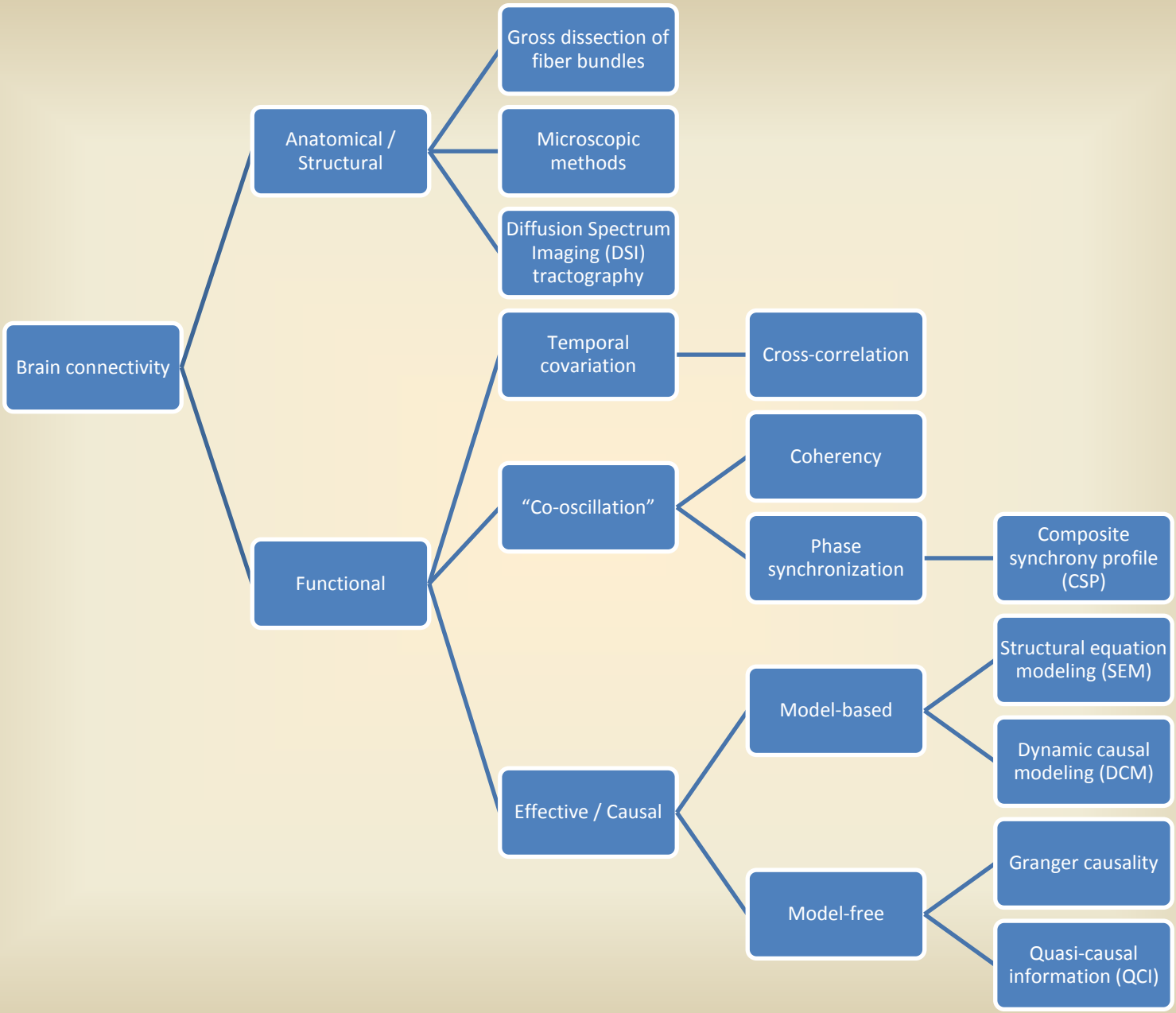
Figure 1.4 Schematic illustration of levels of organization in the nervous system. The spatial scales at which anatomical organizations can be identified varies over many orders of magnitude. Icons to the right represent structures at distinct levels: (top) a subset of visual areas in visual cortex (van Essen and Maunsell 1980); (middle) a network model of how ganglion cells could be connected to simple cells in visual cortex (Hubel and Wiesel, 1962), and (bottom) a chemical synapse (Kandel and Schwartz, 1985). (From Churchland and Sejnowski 1988.)

Churchland PS, Sejnowski TJ. *The Computational Brain.* 1992. p. 11.

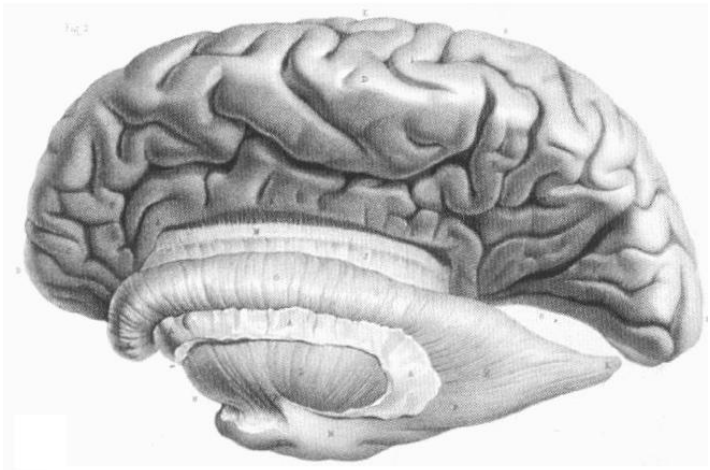
Levels of Organization vs. Levels of Analysis

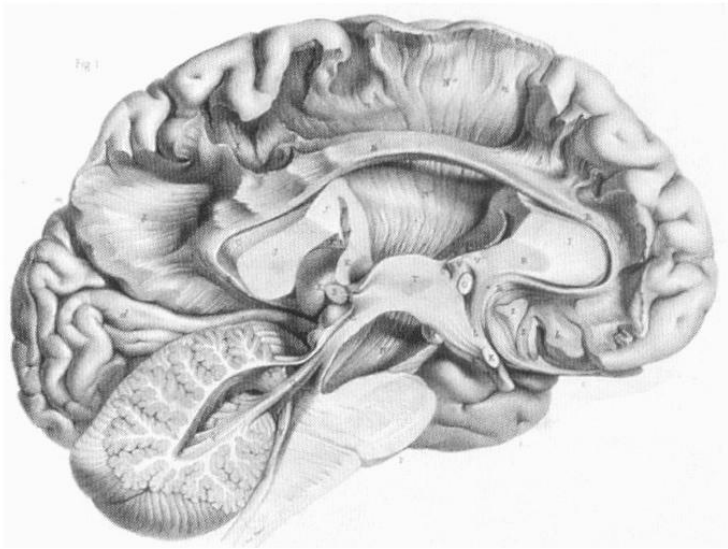
	Physical		*Computational*	
	Structure / Process	Dynamics (Laws)	Algorithm	Function
Organism / Environment	Behavior / Psychophysics	Performance Model	Information / Control Model	Meet Task Demands
CNS / PNS (1 m)	Psychophysiology			Cognition / Action / Evaluation
Systems (10 cm)	Large-Scale Brain Networks			Cooperative Computation
Maps/Areas (1 cm)	Regions of Activation			Local Cortical Processing
Networks (1 mm)				
Neurons (100 μm)				
Synapses / Patches (1 μm)				
Ion Channels (.1 nm)				

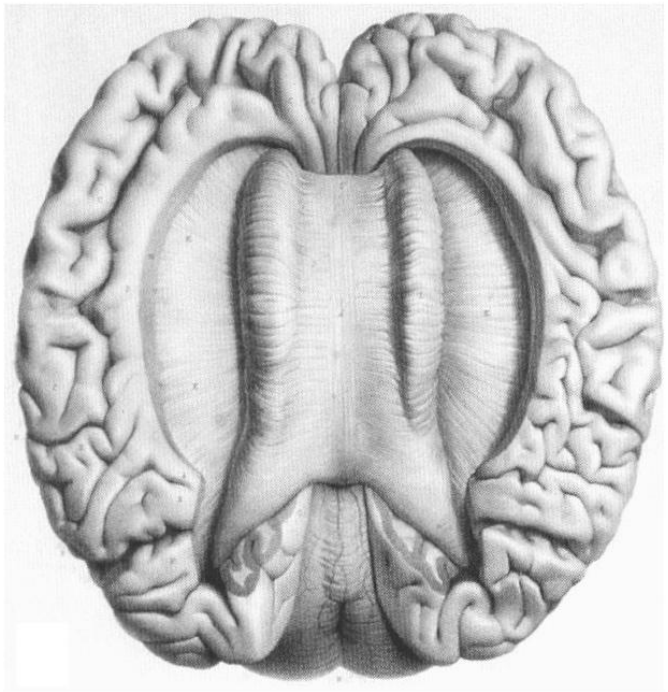
Partially adapted from TJ Sejnowski and PS Churchland (1989): Brain and Cognition. In MI Posner (ed.), *Foundations of Cognitive Science*

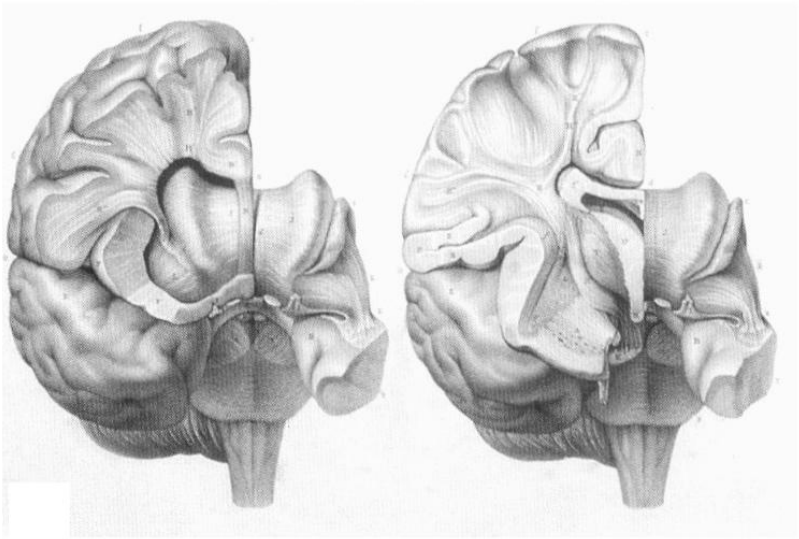

Brain connectivity
Anatomical / Structural
Gross dissection of fiber bundles
Microscopic methods
Diffusion Spectrum Imaging (DSI) tractography
Functional
Temporal covariation
Cross-correlation
"Co-oscillation"
Coherency
Phase synchronization
Composite synchrony profile (CSP)
Effective / Causal
Model-based
Structural equation modeling (SEM)
Dynamic causal modeling (DCM)
Model-free
Granger causality
Quasi-causal information (QCI)

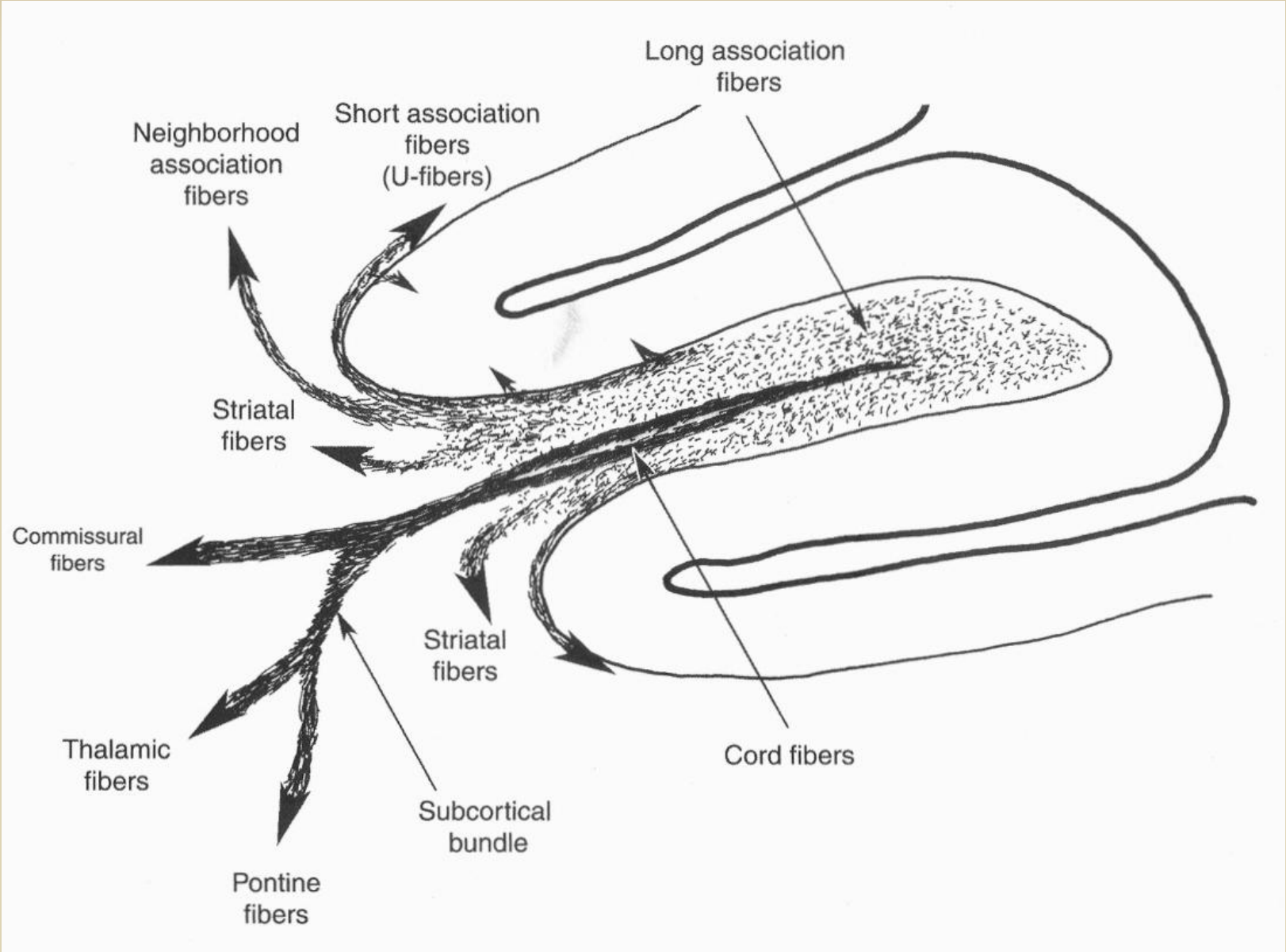
A-L Foville. *Traité complete de l'anatomie*. 1844.





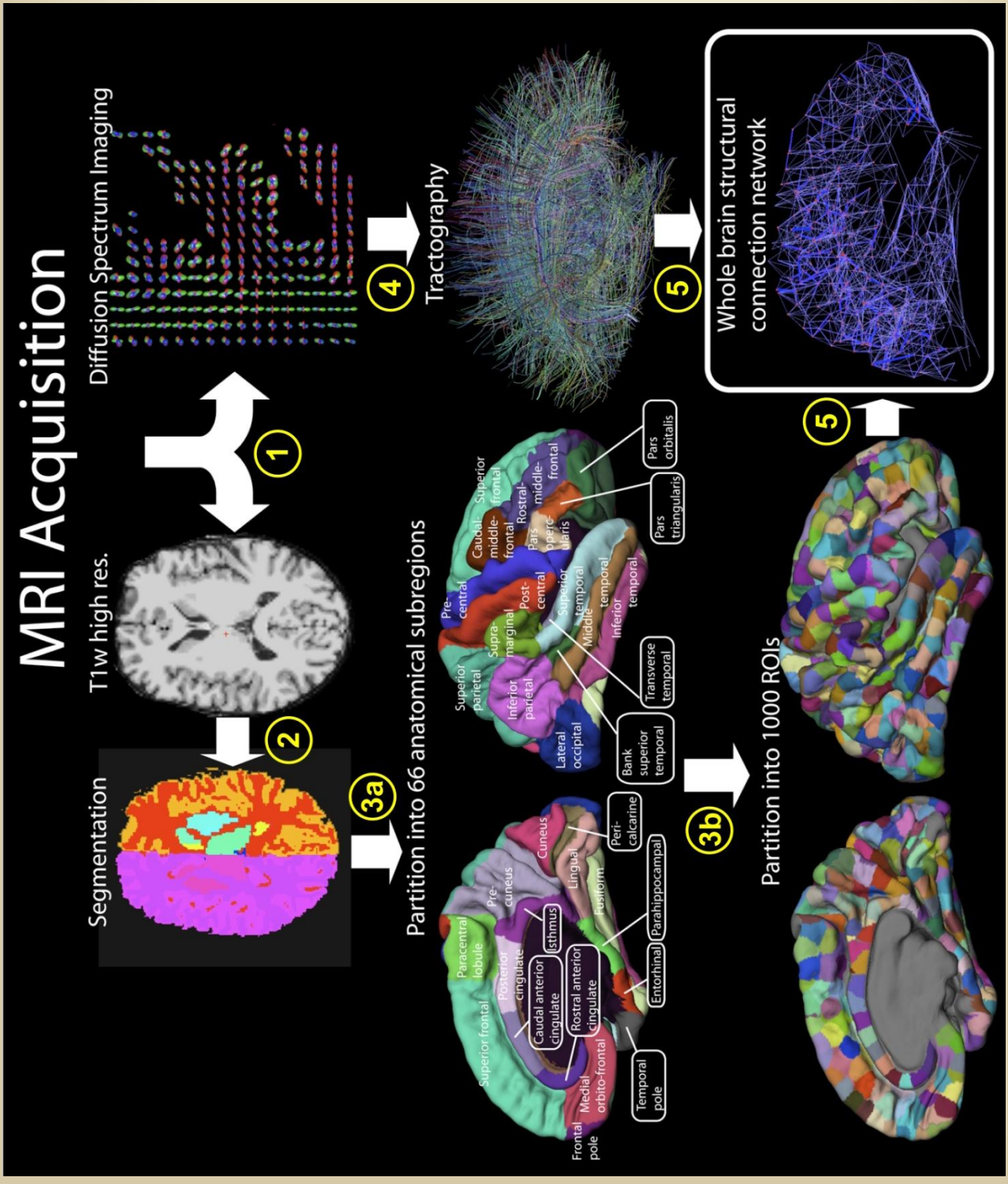






Schmahmann JD, Pandya DN. *Fiber Pathways of the Brain*. 2006. p. 84

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., Friston, K.J. (2008). Mapping the Structural Core of Human Cerebral Cortex. PLoS Biology, 6(7), e159. DOI: 10.1371/journal.pbio.0060159



Human Connectome Project

- NIH Blueprint for Neuroscience Research: $30M
- Systematic collection of noninvasive brain imaging data (DSI tractography, resting state fMRI, EEG/MEG) from 100s of healthy subjects
- “The HCP is truly a grand and critical challenge: to map the wiring diagram of the entire, living human brain.” -Thomas Insel, Director of NIMH
- “Neuroscientists have only a piecemeal understanding of brain connectivity. If we knew more about the connections within the brain—and especially their susceptibility to change—we would know more about brain dysfunction in aging, mental health disorders, addiction and neurological disease.” -Story Landis, Director of NINDS
- Data publicly available in ~5 years

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS 13: 85–95 (2007)

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DISCOVER SOMETHING GREAT

The Study of Autism as a Distributed Disorder

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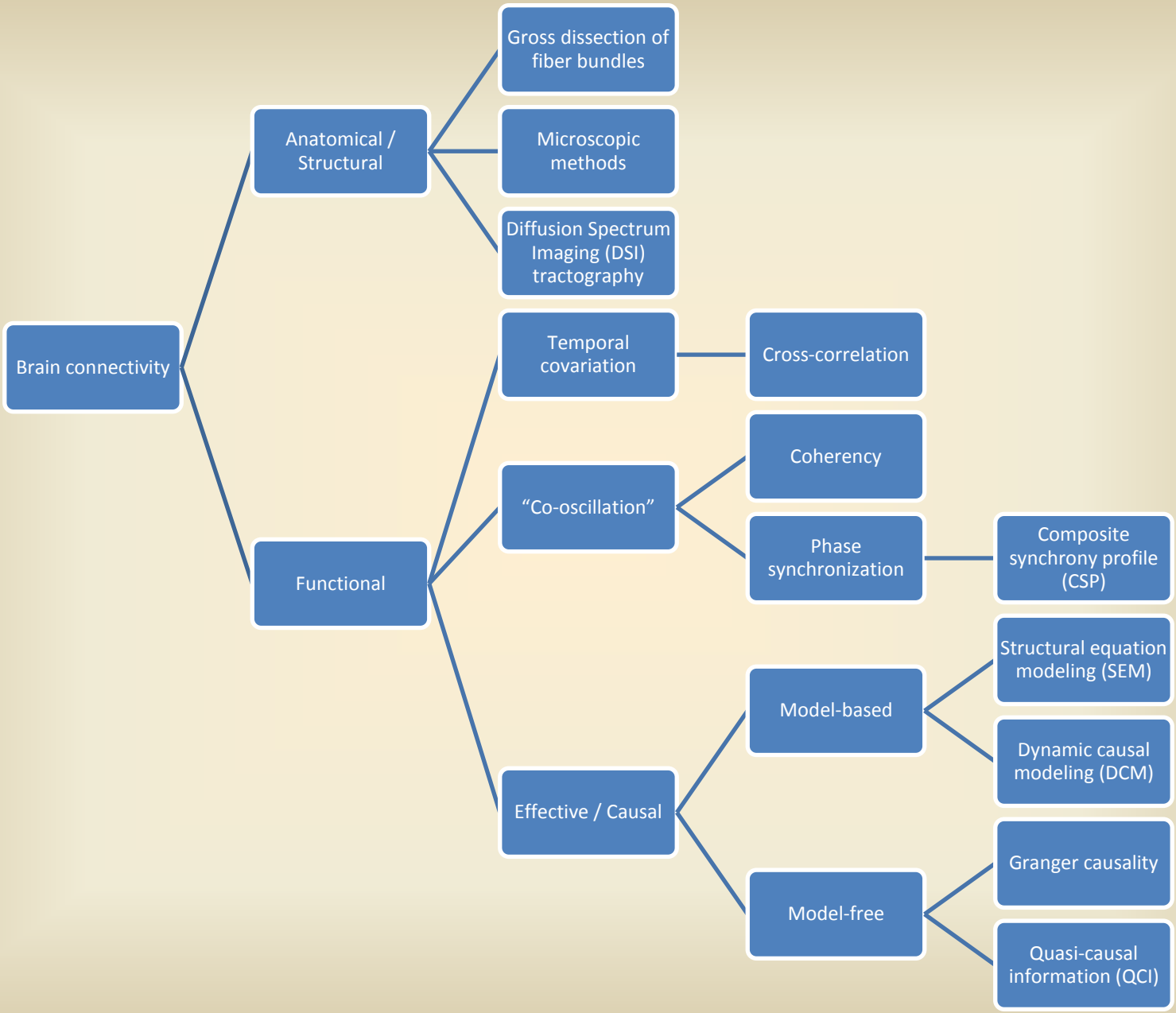
[2]Department of Cognitive Science, University of California, San Diego, California

Past autism research has often been dedicated to tracing the causes of the disorder to a localized neurological abnormality, a single functional network, or a single cognitive-behavioral domain. In this review, I argue that autism is a "distributed disorder" on various levels of study (genetic, neuroanatomical, neurofunctional, behavioral). "Localizing" models are therefore not promising. The large array of potential genetic risk factors suggests that multiple (or all) emerging functional brain networks are affected during early development. This is supported by widespread growth abnormalities throughout the brain. Interactions during development between affected functional networks and atypical experiential effects (associated with atypical behavior) in children with autism further complicate the neurological bases of the disorder, resulting in an "exponentially distributed" profile. Promising approaches to a better characterization of neural endophenotypes in autism are provided by techniques investigating white matter and connectivity, such as MR spectroscopy, diffusion-tensor imaging (DTI), and functional connectivity MRI. According to a recent hypothesis, the autistic brain is generally characterized by "underconnectivity." However, not all findings are consistent with this view. The concepts and methodology of functional connectivity need to be refined and results need to be corroborated by anatomical studies (such as DTI tractography) before definitive conclusions can be drawn.

processes that are present during development. It is this course of developmental events that will ultimately allow a brain region, such as inferior frontal cortex, to participate in a specific set of functions, such as language [for detailed discussion, see Müller, in press-b].

Given this approach, developmental disorders cannot be understood using adult clinical models of lesion-symptom correspondences. The notion of "residual normality," according to which a localized damage removes well-defined components from a functional system, leaving other components intact, has been applied to the mature nervous system, with some—probably debatable—success. Residual normality cannot, however, apply to the developing brain because interactive effects between brain regions and between functional systems are a known fact [see Thomas and Karmiloff-Smith, 2002 for an extensive debunking]. Therefore, it is not surprising that damage to left inferior frontal cortex (Broca's area) or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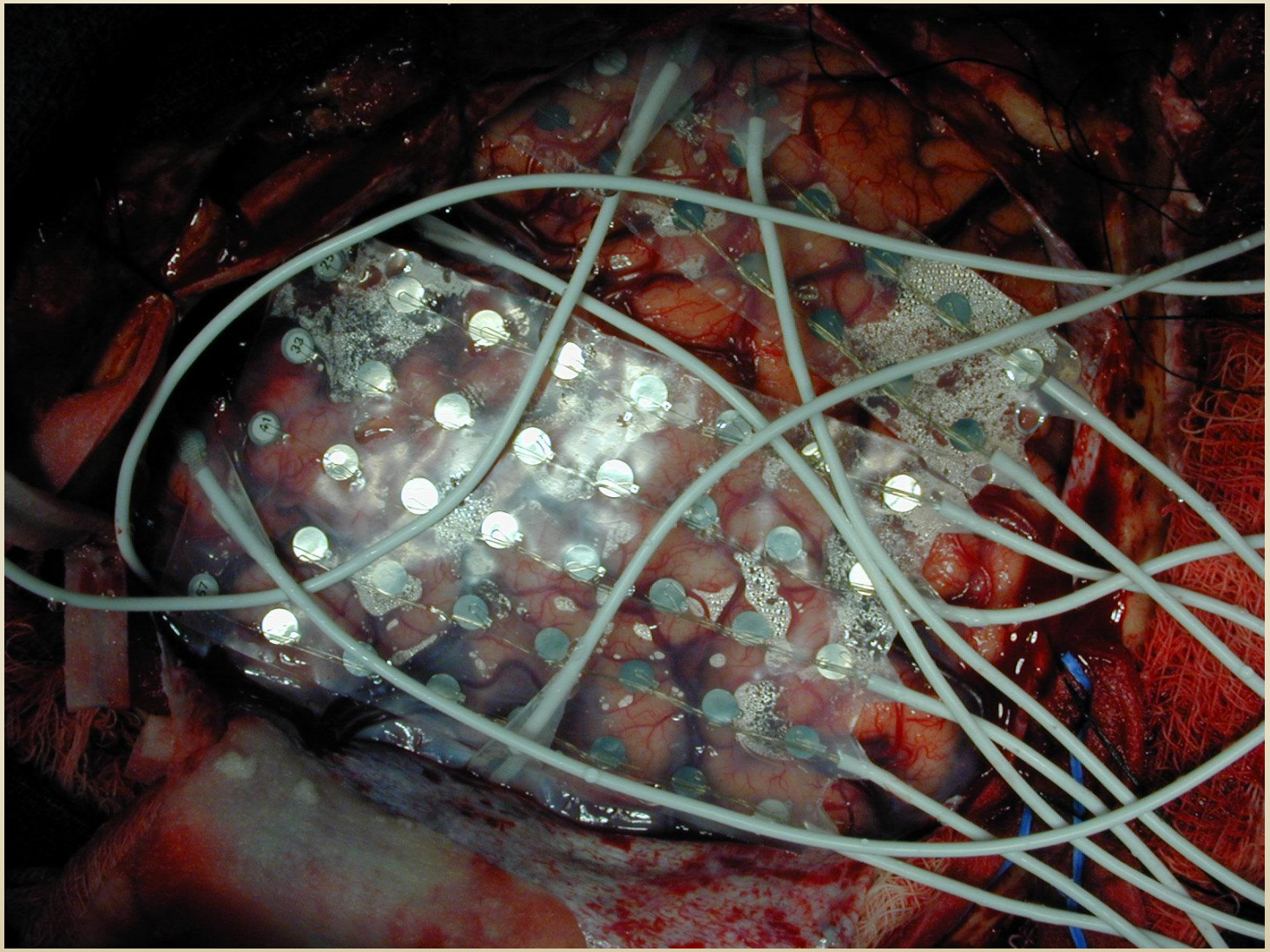
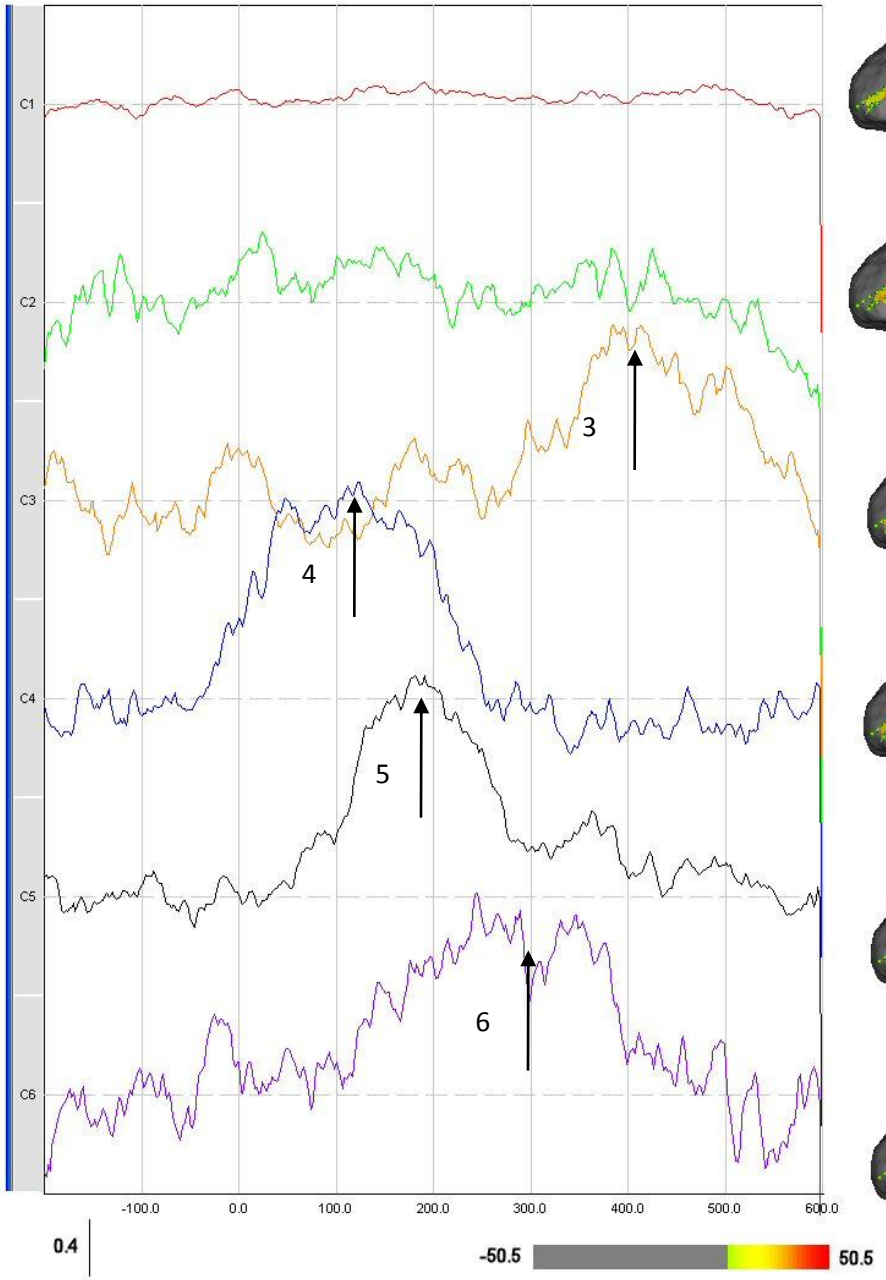
Granger causality
Quasi-causal information (QCI)

Electrocorticography - ECoG



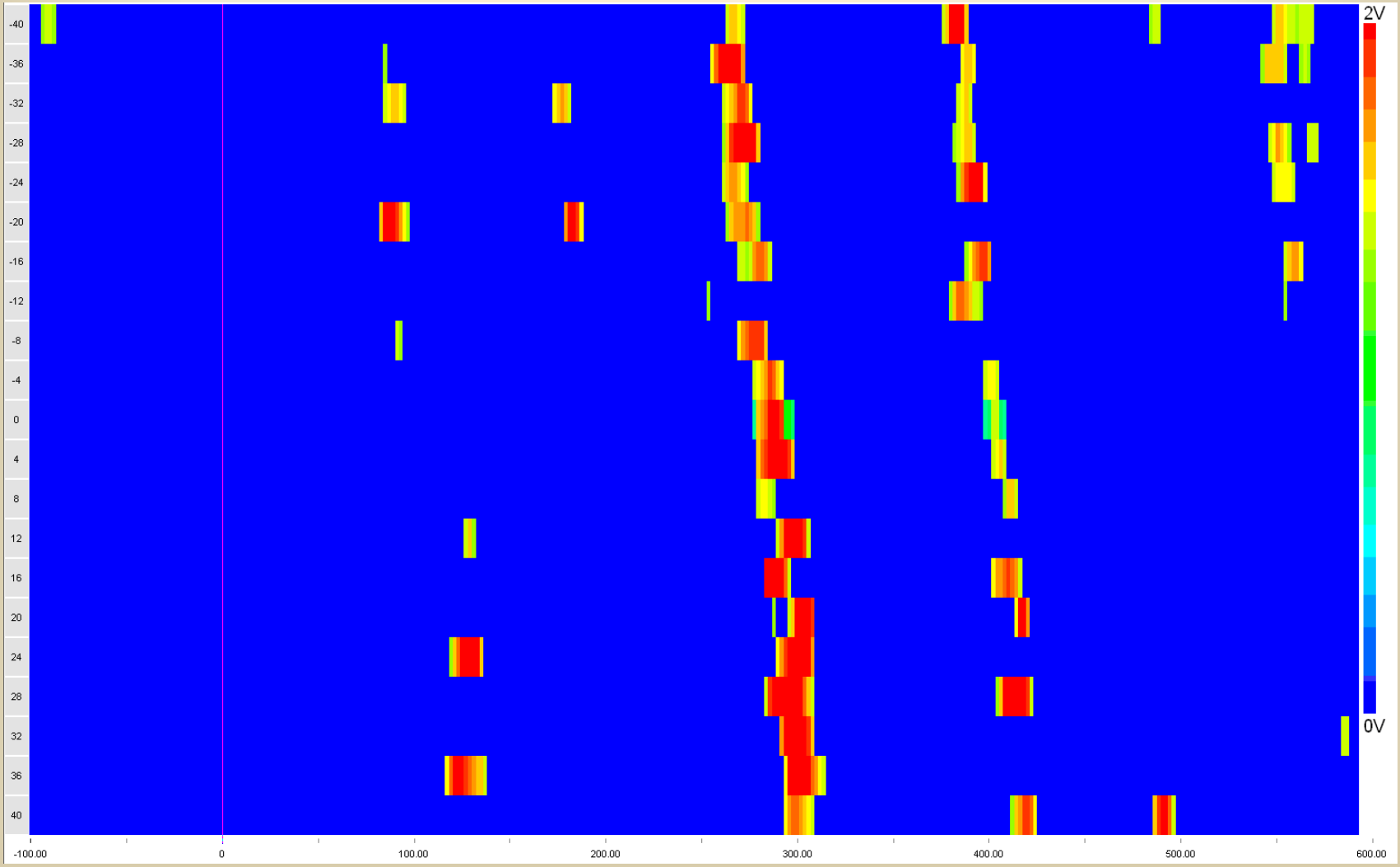
R. Emerson MD, Columbia P&S

PLV/CSP
Event-related ECoG
word recognition task

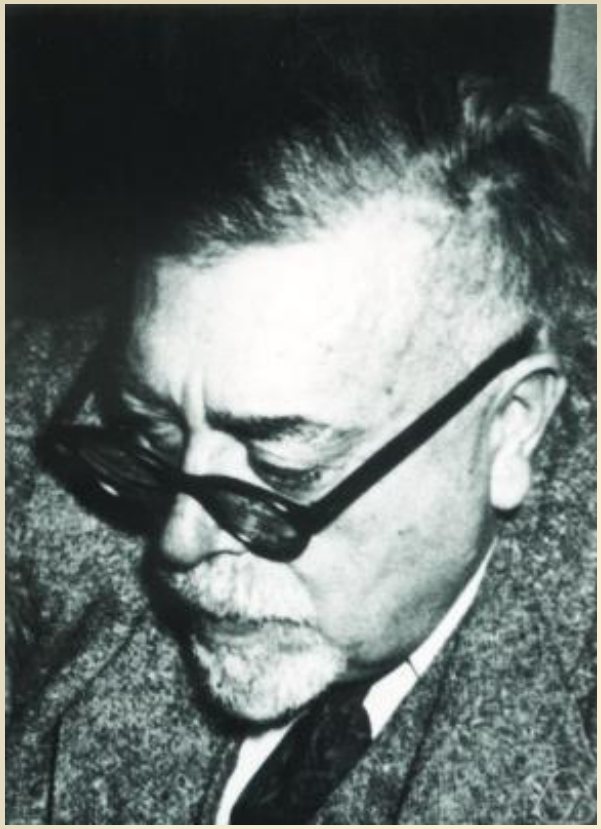


From Richard Greenblatt's CSRC colloquium talk of 10/30; collaboration with Leo Towle & Alex Ossadtchi

QCI – Theta/High Gamma

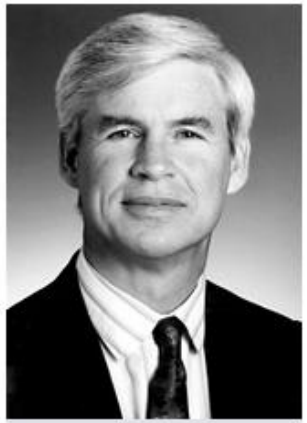


Norbert Wiener



Born	November 26, 1894 Columbia, Missouri, U.S.
Died	March 18, 1964 (aged 69) Stockholm, Sweden
Nationality	American
Fields	Mathematics Cybernetics
Institutions	Massachusetts Institute of Technology

The Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel 2003

"for methods of analyzing economic time series with time -varying volatility (ARCH)"	"for methods of analyzing economic time series with common trends (cointegration)"
	
Robert F. Engle III	**Clive W.J. Granger**
◑ 1/2 of the prize	◑ 1/2 of the prize
USA	United Kingdom
New York University New York, NY, USA	University of California San Diego, CA, USA
b. 1942	b. 1934 d. 2009

nobelprize.org

Wiener-Granger Causality

- “Suppose that we have three terms, X(t), Y(t), and W(t), and that we first attempt to forecast X(t+1) using past terms X(t) and W(t). We then try to forecast X(t+1) using past terms X(t), Y(t), and W(t). If the second forecast is found to be more successful, according to standard cost functions, then the past of Y appears to contain information helpful in forecasting X(t+1) that is not in past X(t) or W(t). In particular, W(t) could be a vector of possible explanatory variables. Thus, Y(t) would ‘Granger cause’ X(t+1) if (a) Y(t) occurs before X(t+1); and (b) it contains information useful in forecasting X(t+1) that is not found in a group of other appropriate variables.” -Clive WJ Granger
- Typically based on linear regression of stochastic processes.
- See: Seth AK (2007): Scholarpedia 2(7):1667.

Quasi-Causal Information (QCI) is a *measure* within a *framework for statistical inference* which addresses the following question:

To what extent is it possible to infer, statistically, effective connectivity *lag spectra* between two brain areas X and Y via *observation only* of neurophysiological time series measured from areas X, Y, and other areas (Z_1, Z_2, …, Z_n), *without strong modeling assumptions* about the network topology or about the functional forms of inter-areal interactions?

Conditional Mutual Information

$$I_p(X,Y \mid Z) \equiv D(p(x,y \mid z) \,\|\, p(x \mid z)p(y \mid z))$$

$$= \mathrm{E}_p\left[\log \frac{p(x,y \mid z)}{p(x \mid z)p(y \mid z)}\right]$$

$$= H_p(X,Z) + H_p(Y,Z) - H_p(Z) - H_p(X,Y,Z)$$

e.g., Cover & Thomas

Linear Entropy Uses Gaussian Probability Densities

$$H_g(\mathbf{X}) = \frac{n}{2}\log(2\pi e) + \frac{1}{2}\sum_{i=1}^{n}\log[\mathbf{C}]_i$$

Shannon

Nonlinear Entropy Uses Non-Gaussian Probability Densities

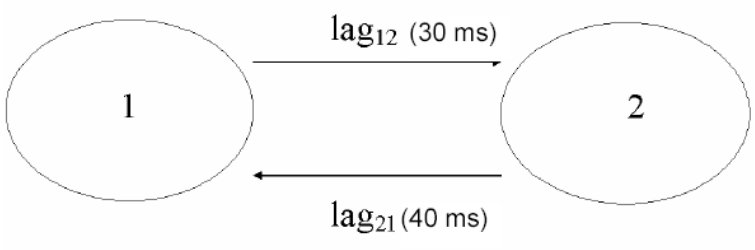
$$H_n(\mathbf{Z}) = -\frac{1}{N}\sum_{i=1}^{N}\log p_i(\mathbf{z}_i)$$

$$= -\frac{1}{N}\sum_{i=1}^{N}\log\left\{\frac{1}{N-1}\sum_{j\neq i}\frac{1}{(2\pi)^{n/2}\sigma^n}\exp\left\{-\frac{|\mathbf{z}_j-\mathbf{z}_i|^2}{2\sigma^2}\right\}\right\}$$

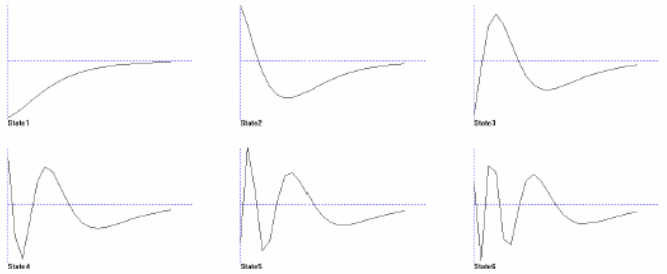
Ivanov-Rozhkova

Linear vs. Nonlinear

$$x_i(t) = \sum_{j=1}^{n}\left(\sum_{k=1}^{p}\alpha_{jik} f_{ji}(x_j(t-k-\tau_{ji})) + \sum_{k=1}^{q}\beta_{jik} g_{ji}(\varepsilon_j(t-k-\tau_{ji}))\right)$$



Singular Spectrum Analysis
state functions



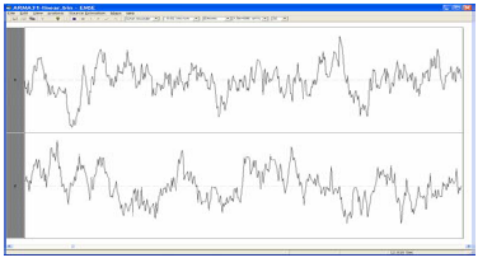
ARMA(3,1)

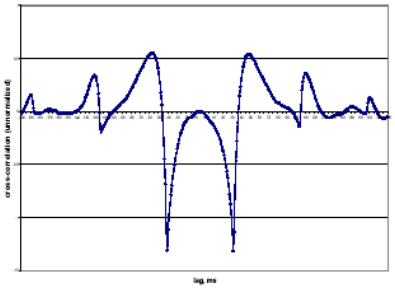
Cross-correlation

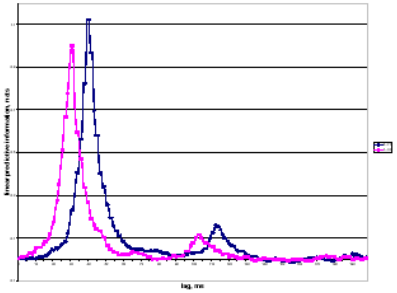
Linear predictive information

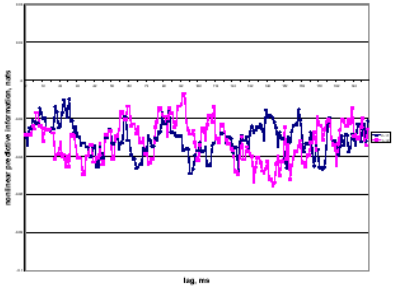
Nonlinear predictive information

$f(x) = x$

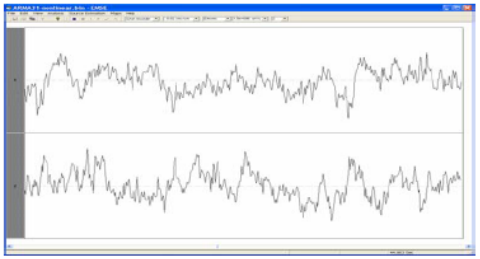


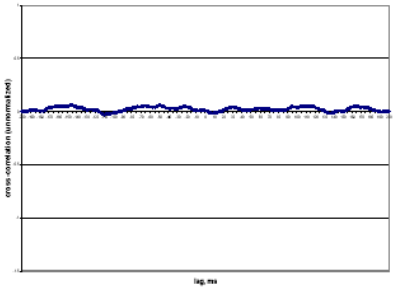


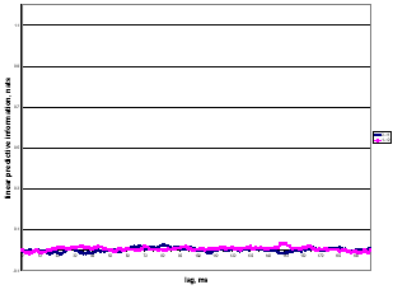


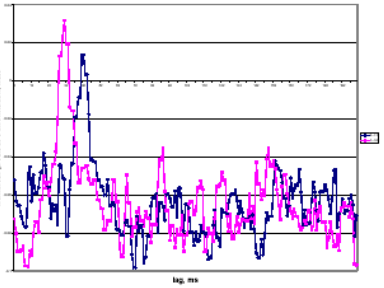


$f(x) = |x|^{0.8}$

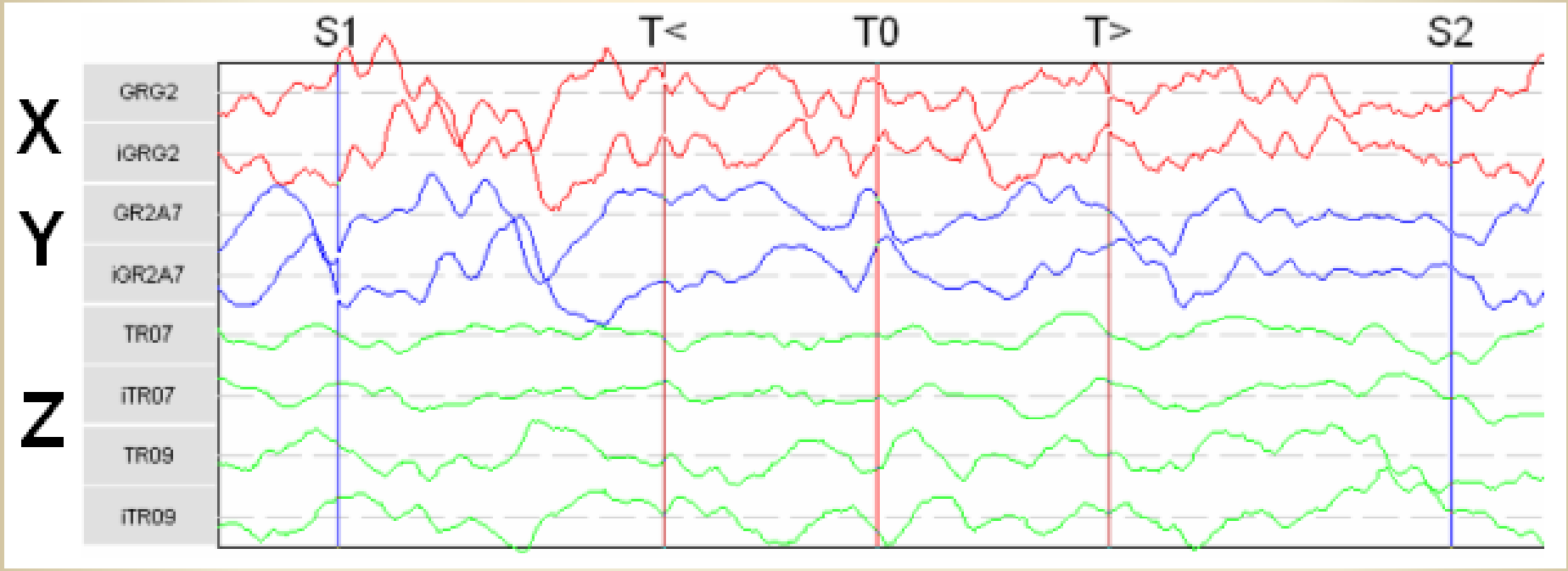








Schema for event-related data and statistical significance testing



- I(X(T<), Y(T>) | X(T>), Y(T<), X(T0), Y(T0), Z())
- I(X(T>), Y(T<) | X(T<), Y(T>), X(T0), Y(T0), Z())
- Null distribution: Destroy causality by randomly interchanging T< and T> across trials

Hippocampus circuit schematic

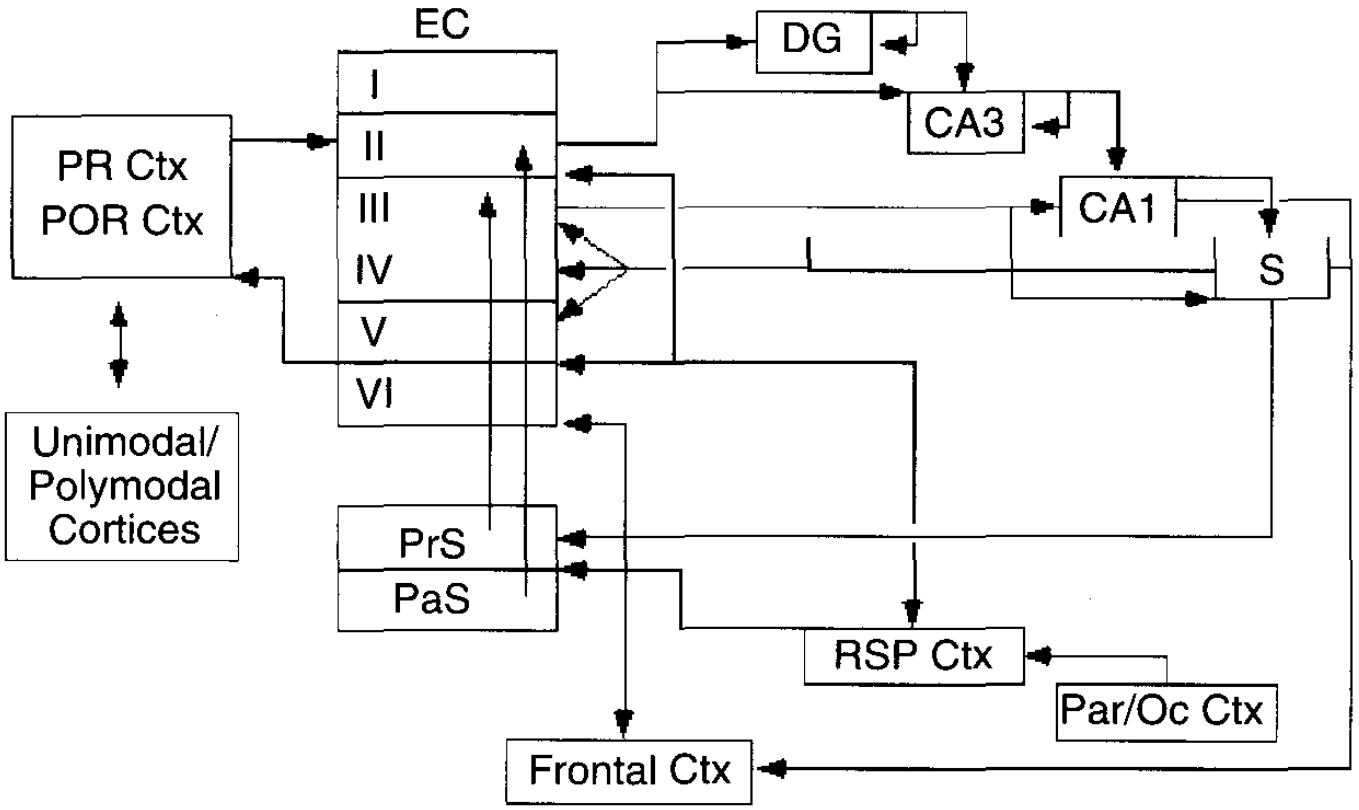
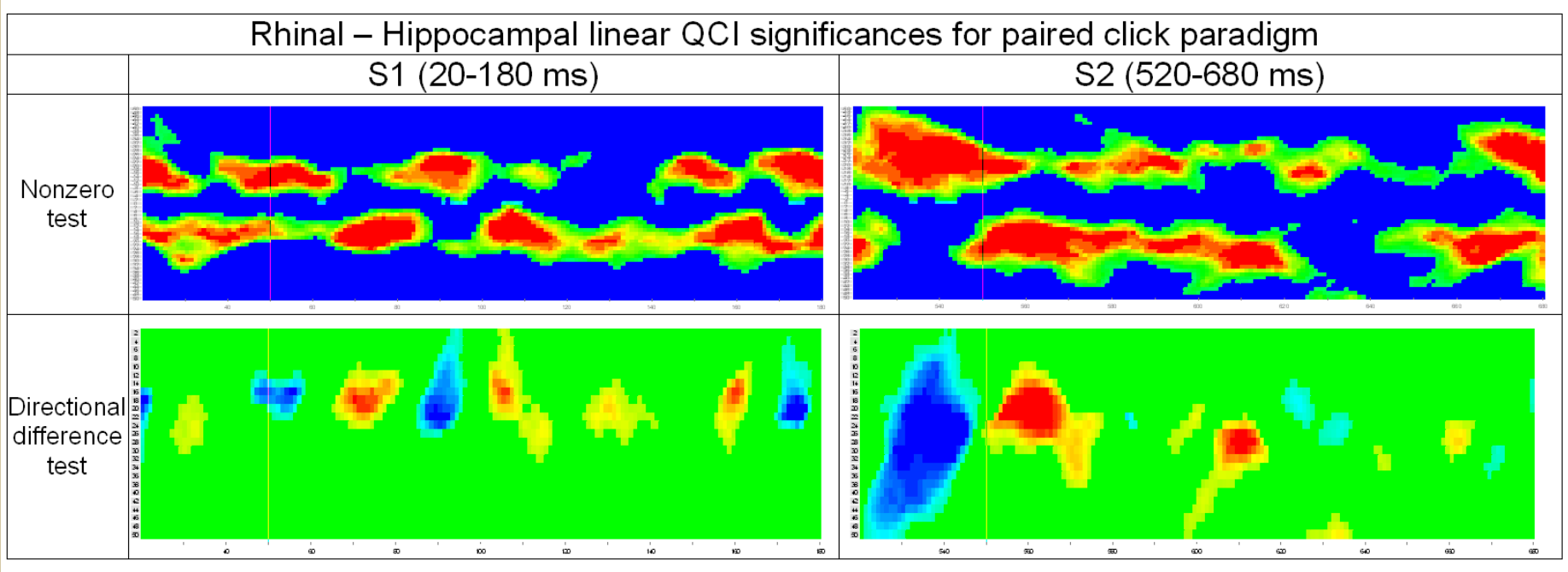


Fig. 11.5. Summary diagram of the major intrinsic connections of the rat hippocampal formation and several of the extrinsic cortical inputs. This diagram emphasizes the serial and parallel aspects of the intrinsic hippocampal circuitry. See text. Abbreviations: DG, dentate gyrus; CA3, CA1 fields of the hippocampus; EC, entorhinal cortex; PR, perirhinal; POR, postrhinal; PrS, presubiculum; PaS, parasubiculum; Par/Oc Ctx, parietal occipital cortices; RSP Ctx, retrosplenial cortex.

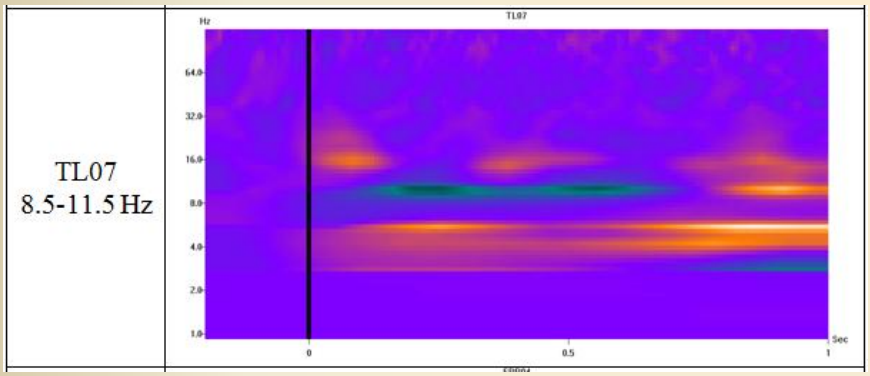
Johnston D, Amaral DG, chap. 11 in GM Shepherd (ed.), *The Synaptic Organization of the Brain* (5th edition), 2004, p. 462.

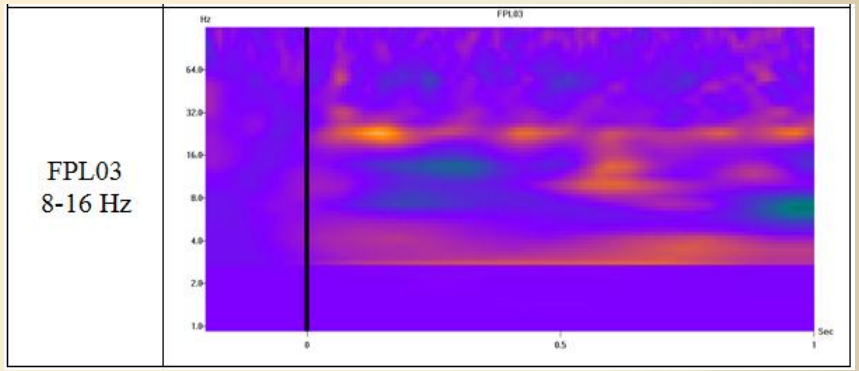
Boutros-Bonn paired click intracranial EEG

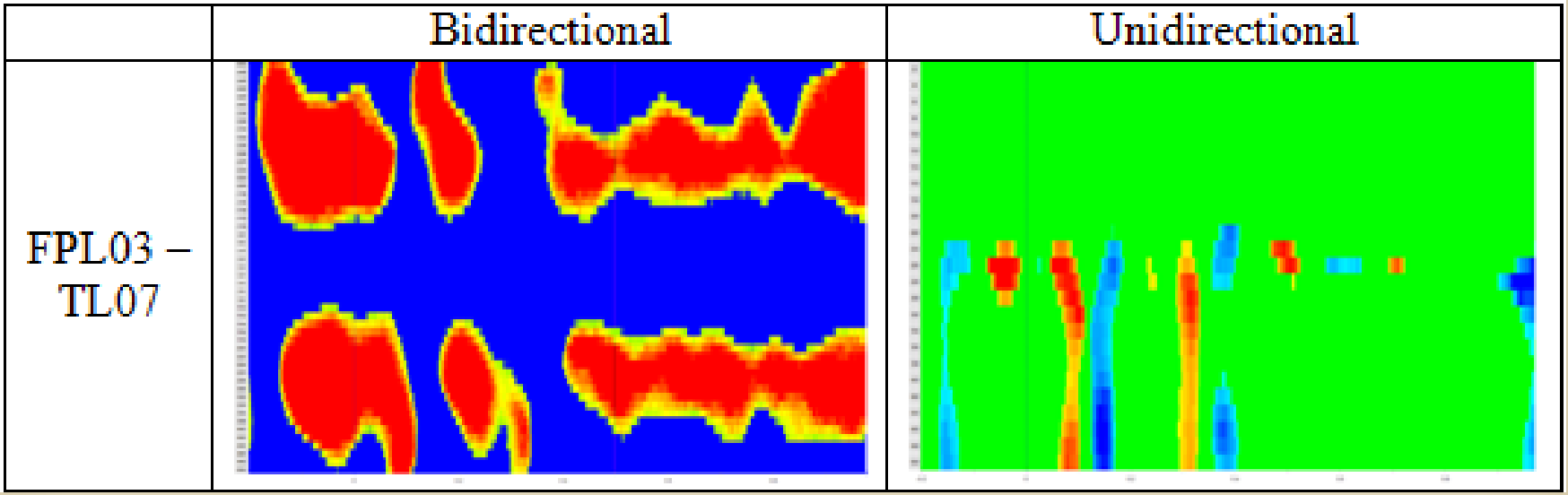


- 100 paired clicks: S1 to S2, 500 ms; S2 to S1, 8 s
- “States”: analytic time series via Hilbert transform
- Linear QCI with minimal confounds

Posterior HPC – Prefrontal, paired click







Repeated pattern. First, prefrontal→HPC at 85 ms flips to HPC→prefrontal at 150 ms. Then again, prefrontal→HPC at 300 ms flips to HPC→prefrontal at 365 ms.

Computational Issues (I)

- Long computation time, especially for randomization statistics
  - Parallel computations for pairs, context, bands, and randomizations
- Combinatorial explosion of possible contexts
  - Limit by known anatomical connections
- How to handle areas not measured, but anatomically connected?
  - Use computational modeling to fill in
  - Incorporate lag information

Computational Issues (II)

- Data mining problem
  - "search for intracranial intelligence"
- Diminishing statistical significance: Multiple comparisons explode as search continues
- Merging results across participants
  - Individual differences probably more variable for functional/effective connectivity
- What can we learn about "communication channels" within brain-wide networks?
  - From physical measures to bio-communicational and bio-computational significance

Ongoing work

- Side-by-side comparison of QCI with Granger causality (Huhn, Erdi)
- Intracranial validation study with CCEP data (Burgess, Enatsu)
- Extracranial-to-intracranial validation study with same patient, same task data (Boutros)
- Cognitive applications (Boutros; Clark, Moores, Greenblatt)
- Epilepsy applications (Towle, Greenblatt, Ossatdchi)