Basics of Neural Networks

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Basics of Neural Network

I. GENERAL CONCEPTS AND TERMS

Connection Basics - Outline

- Explain most common network terms found in the functional imaging literature.
- Discuss parcellation and types of networks.
- Review key regions of interest
- Outline the Development of Networks and how they facilitate perception and cognition (adaptation)
- Review common network configurations relevant the neurofeedback practitioner - or are they?

Additional materials: https://www.dropbox.com/sh/x7oug4d03js4wat/AACx4lXCyFIKk1sgOyZlhDpTa?dl=0

Connection Basics

Current purpose in studying the connectome of the brain is to discover

- The mechanisms of communication between one functional system/network to others, each operating at different/multiple frequencies, orchestrating activity from specific to integrative which underlie the full range of human behavior. This transfers occurs from ventral to dorsal levels, between areas within and across hemispheres.
- How successive integration allows adaptation to events both external and internal to the organism which occur on time scales ranging from at least milliseconds to spanning several days.

Connection Basics

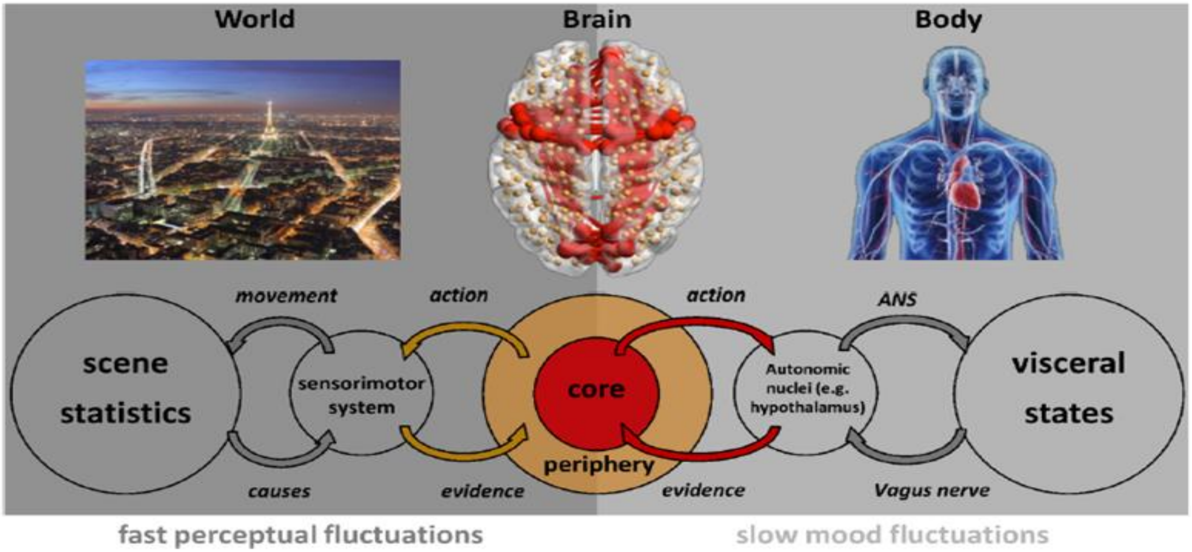
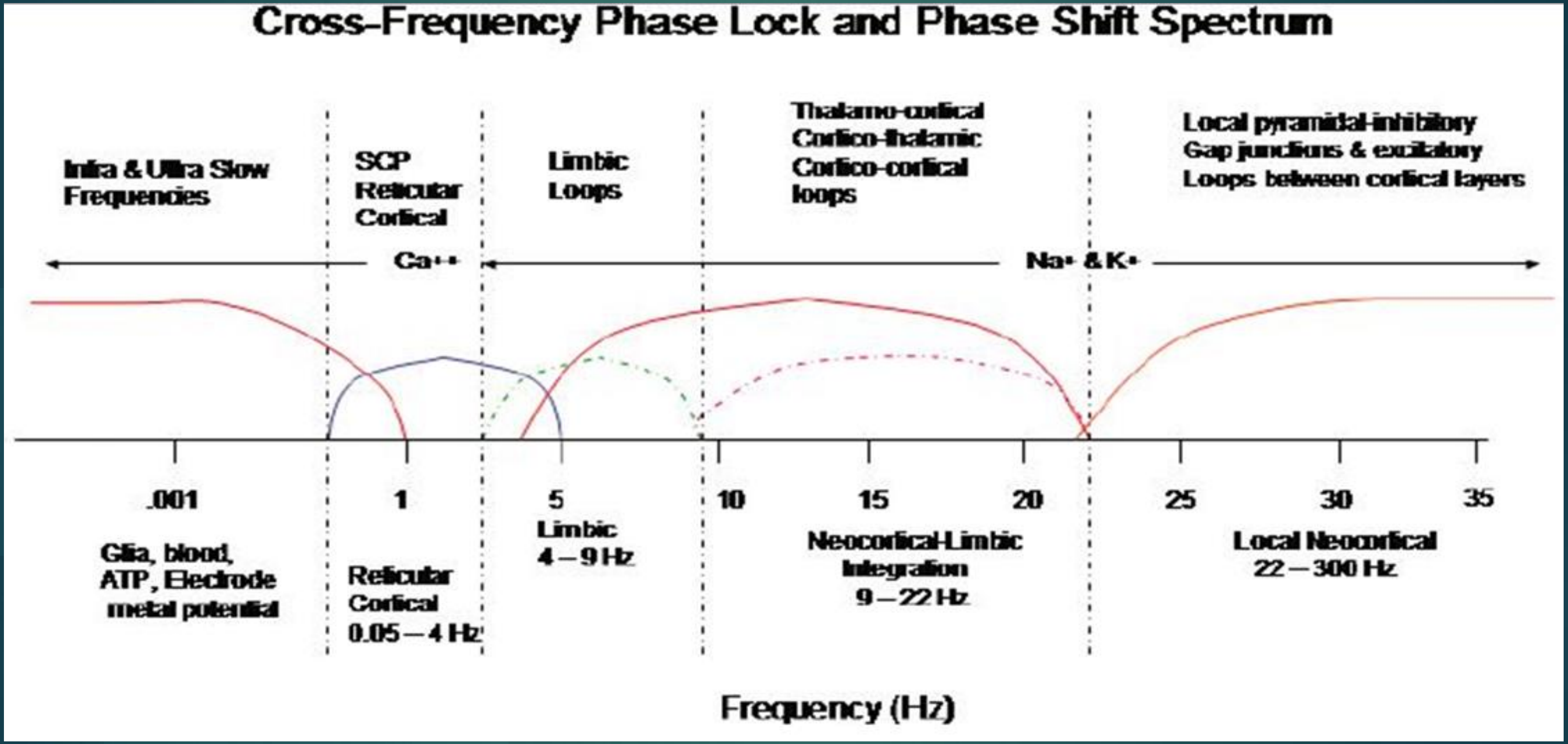


Figure 6. *The brain must cope with interconnected time scales: From fast perceptual to slow mood dynamics. Rapid exteroceptive perception is supported through fast, unstable dynamics in the topological periphery (left hand side). Slow interoceptive perception arises from slow neuronal dynamics within the topological rich club core of the brain (right hand side). Connectome image taken from reference (116).*

Connection Basics



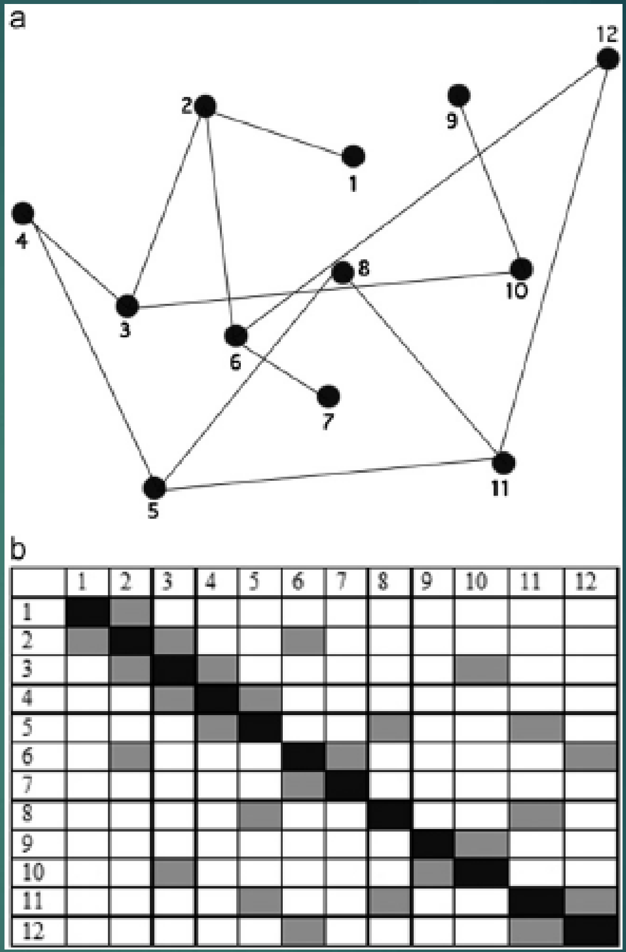
Connection Basics- Terms

A graph can mathematically represent a network as a series of vertices and connecting edges.

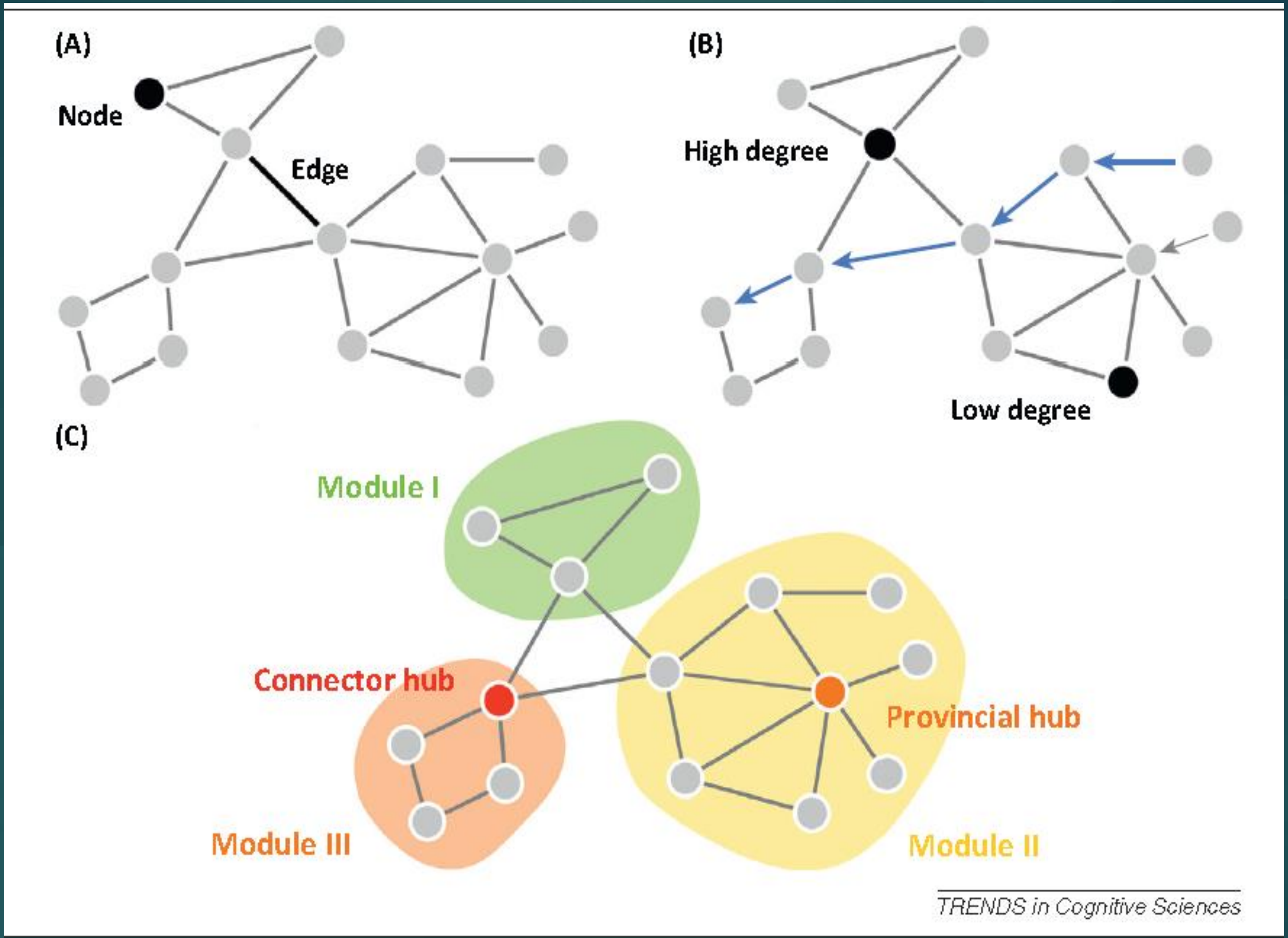
The adjacency matrix lists each vertex and its neighbors.

Directionality, weighting- strength of connection, could be represented

Graph theory is used to describe structure and operational charteristics of a network, detect and quantify subsystems; mapped to functions.



Straaten & Stam, 2013



M.van den Hueval & O. Sporns,2013

Connection Basics-Terms

- Node or vertex is an area of the brain as small as a neuron or much larger region such as a Brodmann area which is connected to other nodes which together form a network(s).
- A module (many neurons) is a group of nodes with a large number of mutual connections within the group and few connections to nodes out of the group.
- Outside connections are to other modules which may serve different functions

Connection Basics-Terms

- The role/importance of a node is described by various measures called centrality measures.

- Nodal degree- “K” is a key centrality measure referring to the number of edges or connections from a node to other nodes(neighbors). Can indicate when a node is a point of relative importance in a network. Hubs are high degree nodes. An average K can also be calculated for a whole network.

- Edges are structural connections between nodes.

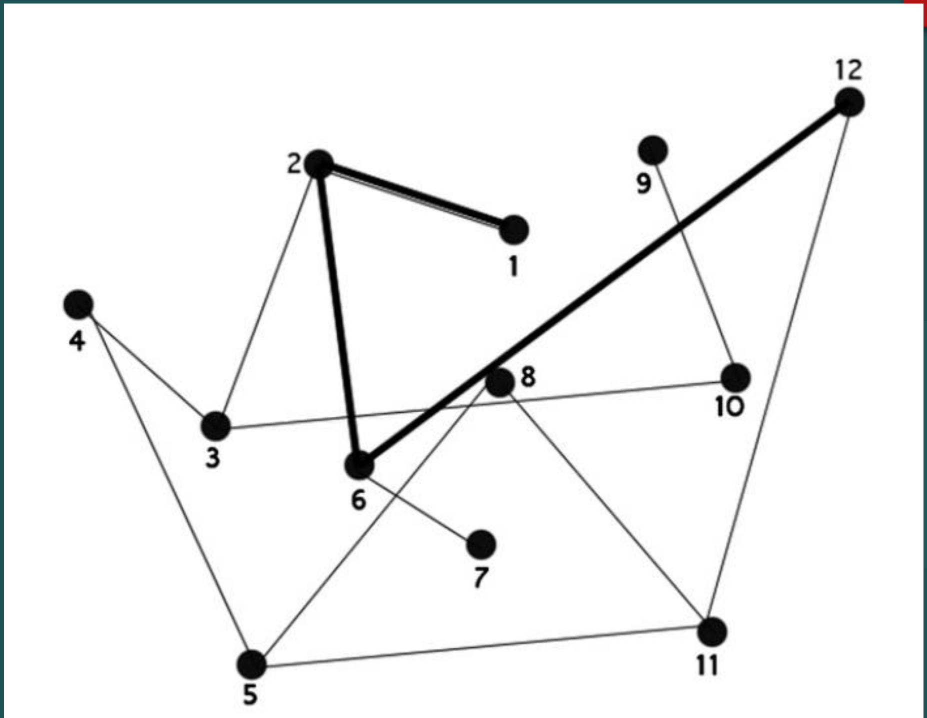
Connection Basics-Terms

- P(k) is the degree distribution of a graph, module, network or system. It is a measure of the probability that a randomly chosen node will have the probability "k."
- The presence of hubs is indicated by a power law degree distribution, i.e. some nodes have an very high degree, and most others have a low degree.

Connection Basics-Terms

"L"

CPL-characteristic path length/ simply path length- "L" is number of vertices involved to get from one node to another; equals number of nodes crossed (involved?) -not actual length of axons or spatial distribution of the nodes. Shorter "L" is held as more efficient; inversely related to IQ



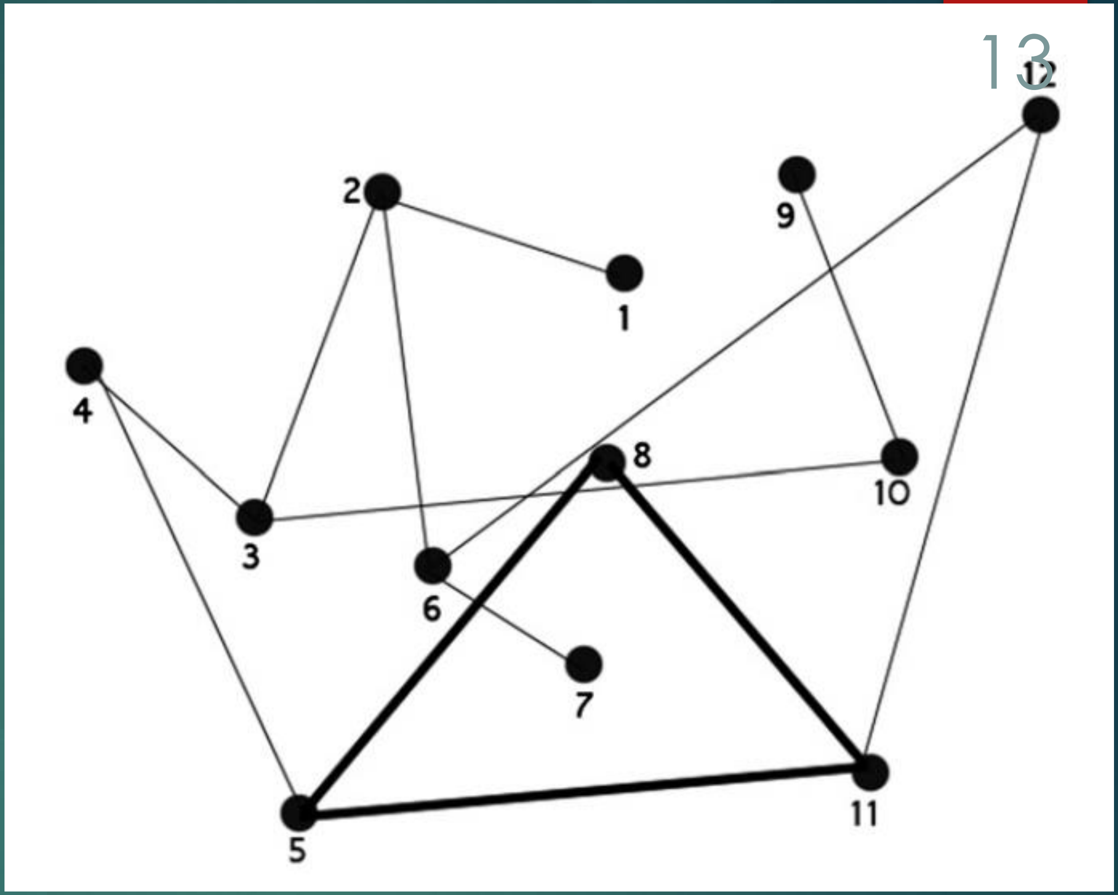
Shortest path from vertex 1 to 12 is 4. L = 4.

Connection Basics-Terms

"C"

Clustering Coefficient

Is a local connectivity measure indicating to what extent the neighboring nodes, to which a node is connected, are connected to each other. Expressed as ratio of actual number of edges (connections) to the number of total possible connections between a nodes neighbors



Vertex 8 has neighbors 5 & 11. "C" is calculated by number of edges between neighbor vertices divided by the total possible number of edges. Thus, C= 1/1= 1.

Connection Basics-Terms

- Closeness centrality is the length of the shortest paths between a node and the rest of the network.

- Betweeness centrality is the number of short communication paths a node participates in. It is defined as the number of shortest paths going through a node or edge. The betweeness centrality is high when the node or edge is used for many shortest paths. This measure can be normalized by dividing it by its maximum value (the total amount of shortest paths in the network). A relative draw- back of this method is that, especially in networks with many nodes, computation time can be long.

Connection Basics-Terms

- Eigenvector centrality allocates a value to each node in the network in such a way that the node receives a large value if it has strong connections with many other nodes that have themselves a central position within the network (Lohmann et al., 2010).

- Thus, connections to important nodes count more, making the nodes with relatively few edges to very important nodes also important (maybe more important than nodes with many edges to less important nodes).

Connection Basics -Terms

- Small worldness (SW)/Sigma is the balance between network integration and differentiation; the ratio of local clustering and the characteristic path length (CPL) of a node relative to the same ratio in a randomized (hypothetical) network.
- Global efficiency -the average shortest path length –i.e. smaller the CPL the more efficient the network. Some authors dispute this finding.
- Regional efficiency is global efficiency computed for each node; related to the clustering coefficient.

Connection Basics-Terms

Review

Most frequently referred to:

K- degree

P(k) degree distribution

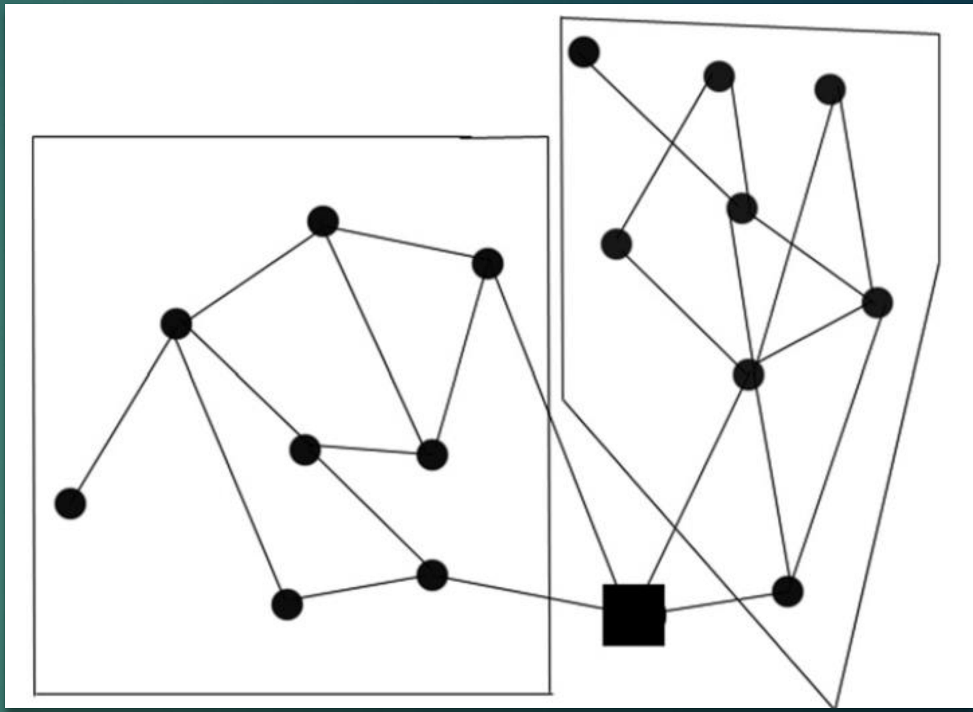
L –path length

C- clustering coefficient

Also: Sigma (a cumulative metric) = the ratio of normalized clustering coefficient to the characteristic path length, a measure of small-world organization.

Two modules- groups of vertices with high interconnectivity with connector hub (black square).

Modularity (MOD) is the degree a system can be divided into smaller networks.

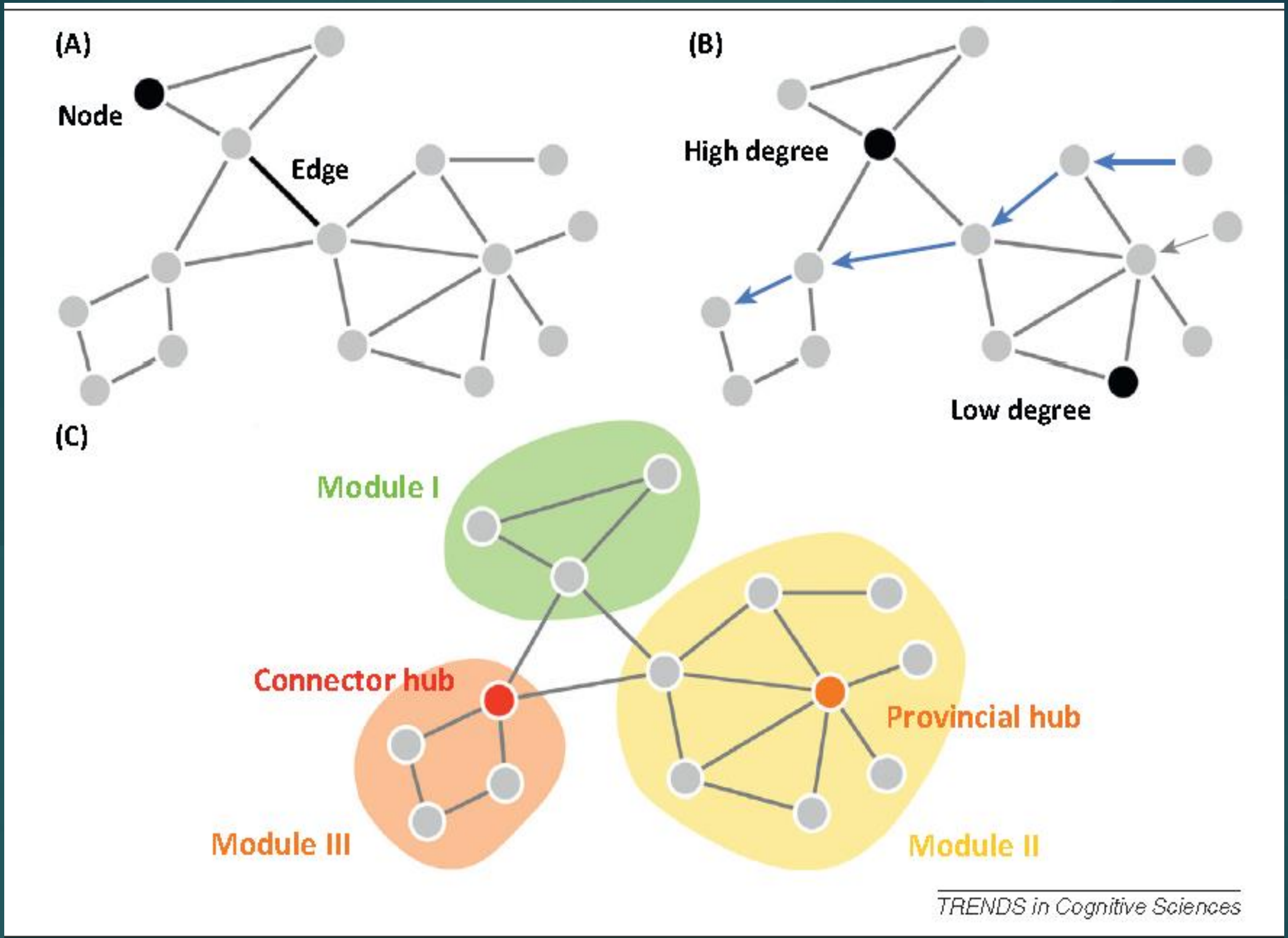


Connection Basics-Terms

- Hubs are nodes/vertices which play a central role in the overall function of a network. Two major hub types are connector hubs and provincial hubs.

- Connector hubs are hubs which have a broad array of connections between modules within a network or connections between networks.

- Provincial hubs are also high degree nodes but which connect to other nodes within the same module.



M.van den Hueval & O. Sporns,2013

Connection Basics-Terms

- Degree correlation- the extent to which nodes of the same or different degree are connected to each other.
- Assortative- when nodes show tendency to connect with nodes of the same degree
- Disassortative- when nodes show tendency to connect with nodes of different degree.
- At macroscopic level(EEG, MEG, fMRI) brain is assortatively organized; disassortative at neuronal level.

Connection Basics-Terms

- Rich club is example of nodes with high assortativity.
- Level of parcellation influences this metric. Complex modular networks are likely assortative
- High degree nodes serve as connector hubs for integration of locally processed information.
- At macroscopic level assortativity may arise from the way the network is formed: by modulation based on synchronization rather than growth. (Stam,2010)

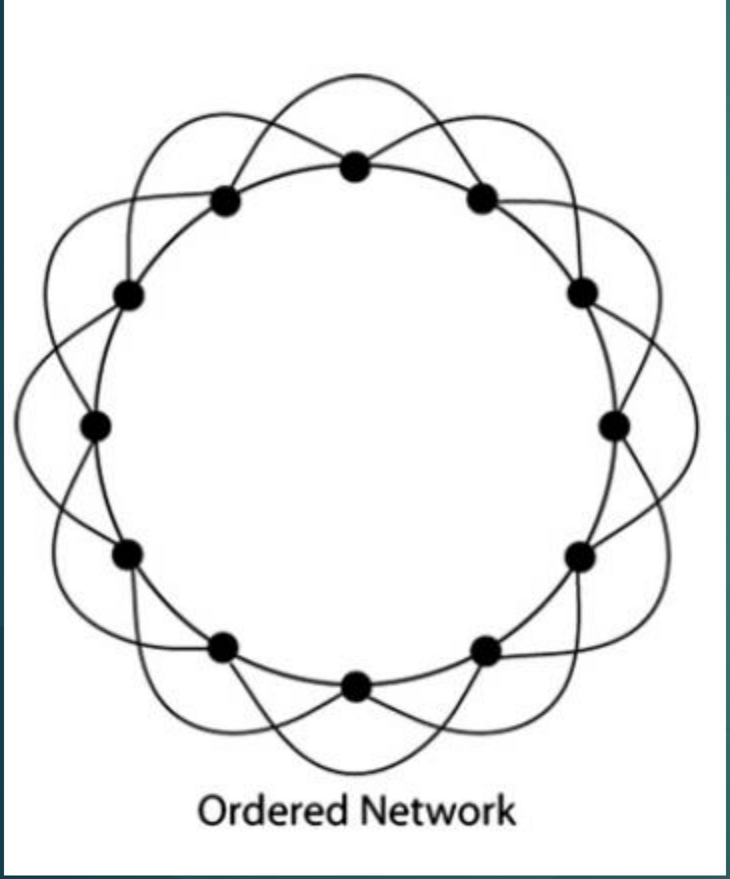
Connection Basics-Terms

- Modules/motifs(brief spatio-temporal patterning) –see slide 18- sub grouping of nodes-edges (graph) can be momentarily accessed (microstate) for a particular function

- Modules/subsystems can be hierarchically organized; subsystems within subsystems allowing for functional specialization and finer differentiation.

- Higher order system can influence a subsystem without affecting its own intrinsic function.

Connection Basics- Network Types

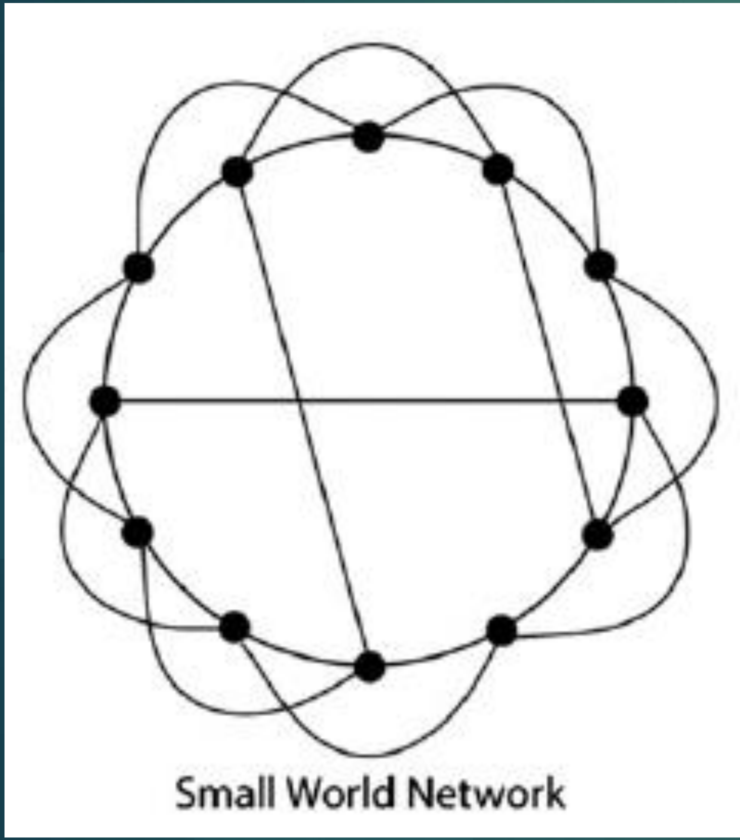


- Each node only connected to its nearest neighbors
- C =high- only connections to neighbors
- L= high, takes many steps to reach distant node

Types fr. Watts & Strogatz, 1998

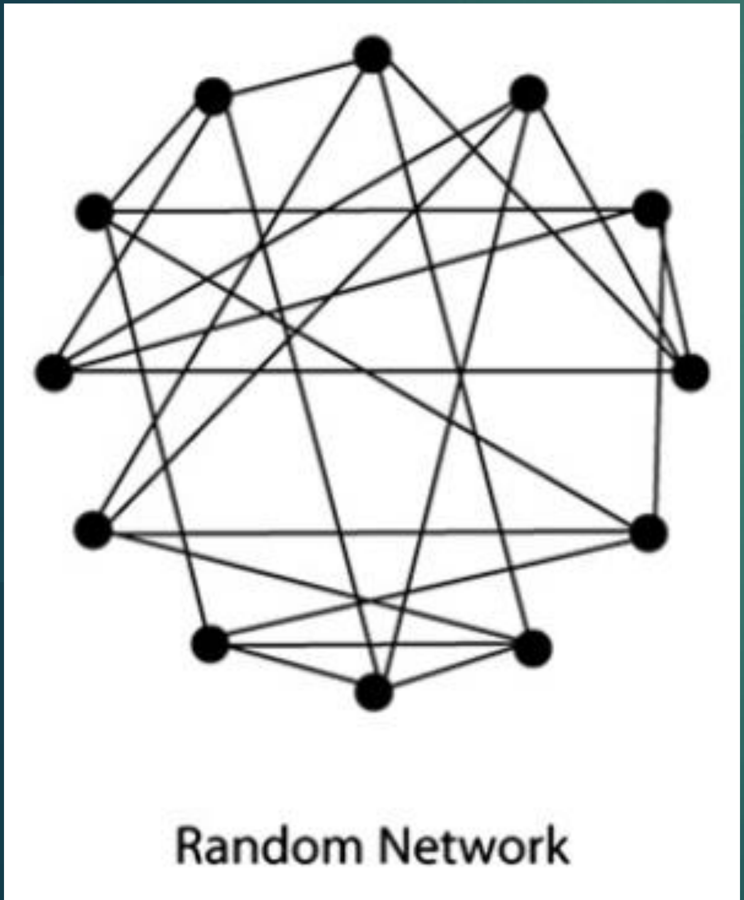
Connection Basics-Network Types

Small World



- With probability p randomly rewire a few edges
- L is lowered
- C remains high
- Complex adaptive system requires Small World network & noise or unpredictability
- Matches neural & social networks more precisely than ordered or random
- Human cortex is Small World

Connection Basics- Network Types

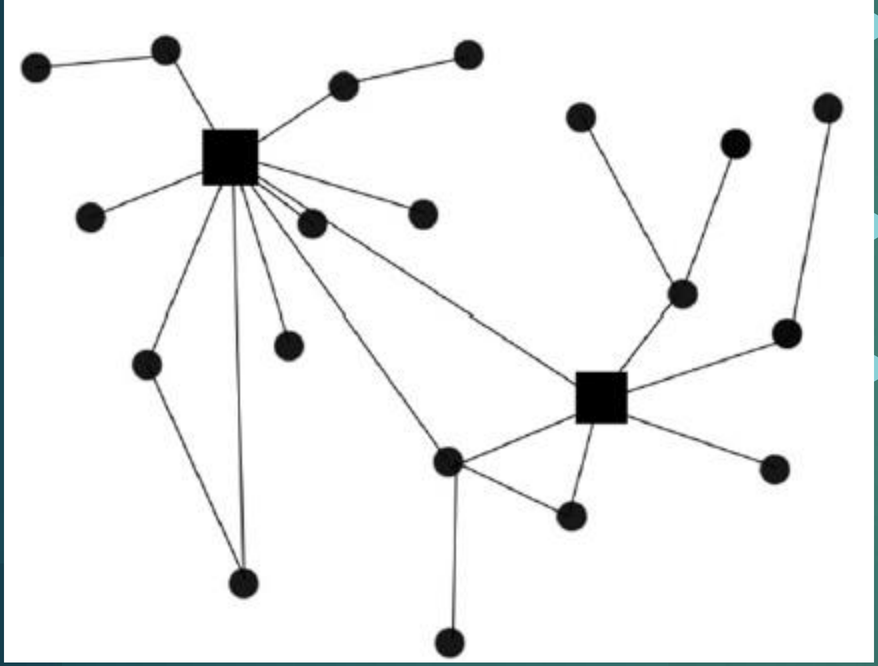


- Increase p and set it equal for every combination of two nodes
- C & L drop to low value
- Hippocampus has random organization
- Cerebellum has parallel organization- no reenterant loops.

Erdos & Renyi, 1959

Connection Basics- Network Types

Scale Free



Scale Free Network

- Probability of new connection depends on node degree K
- Higher K node has higher p
- Produces a scale free network or power law distribution when-Few nodes with high K, many nodes with low K

Connection Basics-Structure Implications

- For the brain to function as a complex adaptive system it must have small world organization and noise/variance.
- Some neurofeedback practitioners question whether constraint of overall variance occurs by training excessive metrics with restricted criteria. Should one consider whether a dynamical system would be limited and adaptation to the training conditions degraded when a certain number of training parameters is exceeded?
- Question then--- Do we limit metrics and areas targeted for training whether surface or (s)Loreta
- Consider the possible influence of the number of metrics/constraints employed in training for optimal outcome may relate to the degree of controllability that a ROI evidences on associated networks

Connection Basics

- Modern analysis shows that functions are widely distributed via grouping of areas from local to long distance networks (Cf. Catani & Theibaut de Shotten, 2012)

- The number of and variety of networks determined from structural analysis and functional analysis depend on which metrics used and inclusion parameter values set and whether the data was taken under at rest or at task conditions.

- Refer to van den Heuvel & Sporns article re Rich Club; or articles by Raichle, Hagmann, Laird, Sridharan, van den Heuval, Sporns, Ye, Gollo, Marqui, Meehan, Catani & Theibaut de Schotten, Mesulam, Leech, Menon and numerous others. A few representative examples are shown below. (See Dropbox link for several structural and functional networks; key areas, network relationship titration **https://www.dropbox.com/sh/x7oug4d03js4wat/AACx4lXCyFIKk1sgOyZlhDpTa?dl=0**)

- Some networks are referred to as resting state networks and others called demand or at task networks. There can be significant overlap but structure does not account for all functional networks (Honey et al., 2009).

- Full understanding of network behavior requires an understanding of distribution, timing, and integration of information in the service of cognition, behavior and emotion

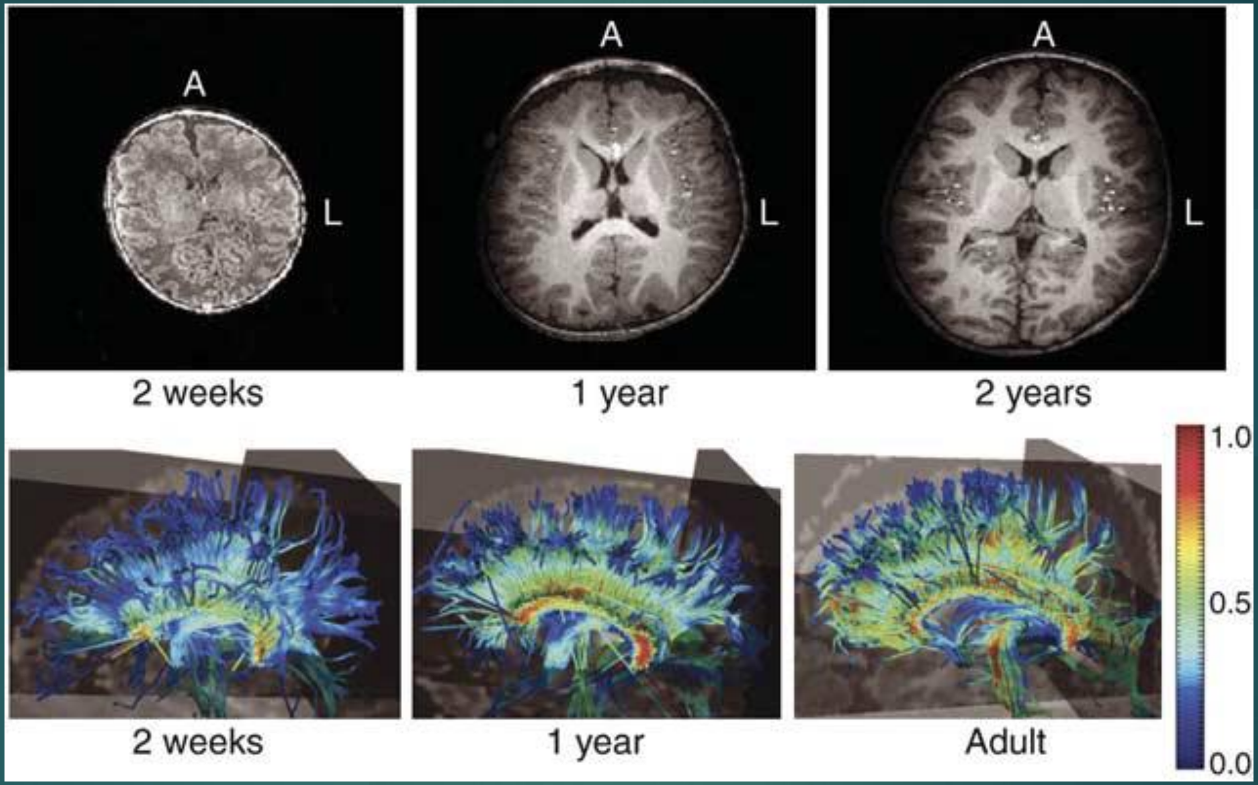
Basics of Neural Network

II. DEVELOPMENT AND COMMUNICATIONS

Organization

- Localized neural circuit developmental and organization “builds” networks which progressively become more complex and hierarchical over time to assimilate accumulative knowledge and promote “precognition” to facilitate “efficiency”.

The Basics Brain Development


A
L
2 weeks
A
L
1 year
A
L
2 years
2 weeks
1 year
Adult
1.0
0.5
0.0

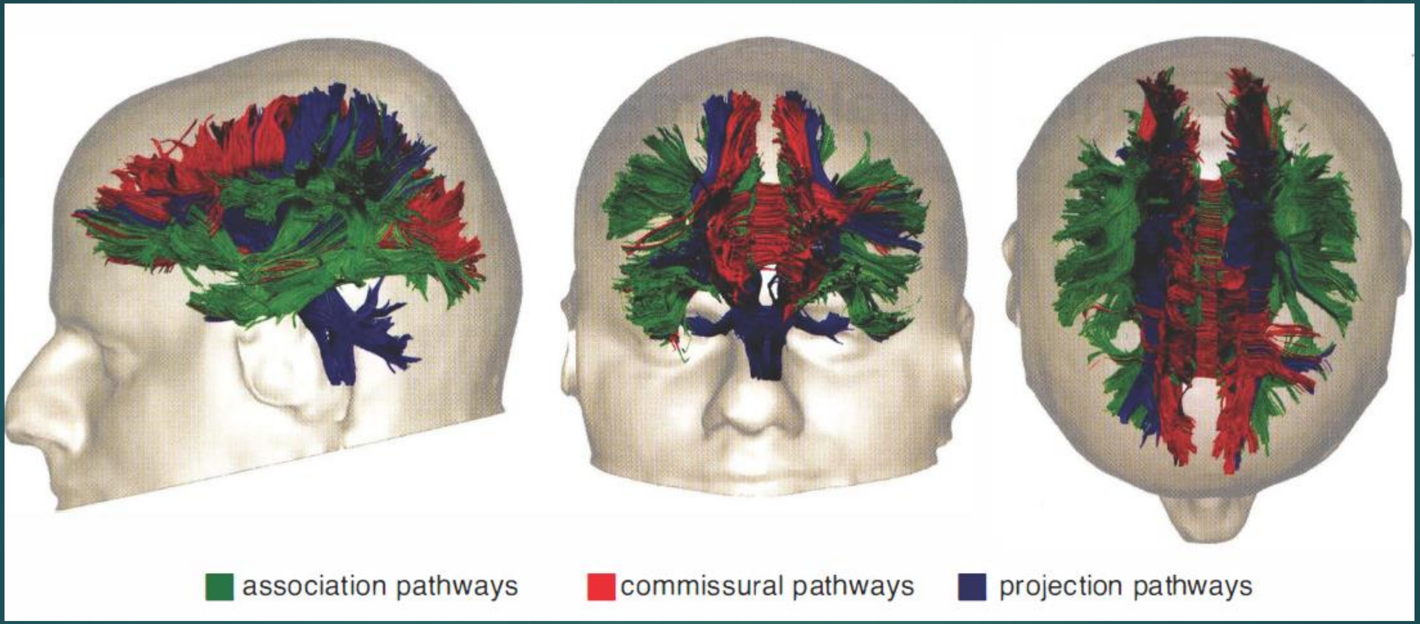
Timeline of Changes

- Differentiation of the neural tube occurs from GA 4 to 12 weeks with new neurons formed in proliferative zones
- Between GA 12 and 20 weeks, the neurons multiply followed by migration to cortical destinations
- Around GA 29 weeks, the process of myelination starts at the brain stem and continues generally in an inferior-to-superior and posterior-to-anterior path
- Between 2 and 7 postnatal years, it is unclear whether synaptogenesis is balanced by elimination of cells and synapses
- Myelination of proximal pathways tends to occur first, followed by myelination of distal pathways
- Cortical myelination seems to mirror functional development
- Maturational trajectories, with sensory tracts myelinating before motor tracts accompanied by protracted myelination of association tracts

- The term ‘connectivity’ encompasses several concepts in neuroscience. **Structural connectivity** describes the physical link—the long range connections formed by white matter tracts.
- On the other hand, **Functional connectivity** describes statistical association of functional signals between brain areas observed through various functional imaging approaches, including functional MRI (fMRI), electro- and magneto-encephalography (EEG, MEG), and fluorodeoxyglucose (18F) positron emission tomography (FDG-PET).

- The differential development of major white matter tracts is also accompanied by a developmental shift in their inter-tract microstructural correlation from a more random state to a more organized state, suggesting refinement of white matter organization with maturation (Mishra et al., 2013).

Connection Basics - Developmental



Connection Basics - Developmental

- Brain continues to mature through the 20s(Gogtay et al, 2004) well into the 30s (Lebel et al 2011).

- Developmental network remodeling shows decreased grey mater density, due esp to short range connection synaptic pruning and increase myelination occuring throughout life. (Hagmann, 2010), (Bartzokis, 2004).

- Remodeling seen in terms of decreased path length, small worldness, clustering, modularity, and fiber density—specific to hemisphere; into adulthood.

Connection Basics - Developmental

- Fiber connection, nodal degree, and nodal efficiency in frontal cortex decreased fr 12-30 yrs; high increase in temporal and parietal areas.
- Consistent with development of executive functions and long range anterior-posterior increased communication.
- Differential trends-left hemisphere shows increased clustering, modularity, and global efficiency(shorter characteristic path length).

Defining Structural Connectivity Leading to Functional Connectivity

- There is no standardized generally accepted anatomical definition of a node or edge (Meehan & Bressler,2012)
- Many "imaging" modalities in identifying nodes use different measures—metabolic (PET), blood (MRI,fMRI,rs-fcMRI), spectral power (LFP, EcoG, EEG, MEG)
- Time domain of MRI is several seconds, EEG –milliseconds; hence different resolution due to time dampening
- Correlation of heightened activity (under task) of a node identified by one modality not fully understood how relates to node identified by different modality. Various advantages- model constructions from each (Zalesky et. a. 2010)
- Network not simply defined by co-activated nodes, must also identify edge
- Node could be defined not only by co-activity but by increased correlation with other node while activation remains constant
- Use of different values for parameters results in different nodes and connectivity patterns, determines to which network(s) a nodal areas is associated
- Measure of single neural unit spiking identifies that 30% of neurons associated with network function are found outside of network itself ; suggests that nodal boundaries are more diffuse than defined by fMRI & function more broadly distributed

Brain connectivity in normally developing children and adolescents

Budhachandra S. Khundrakpam, John D. Lewis, Lu Zhao, François Chouinard-Decorte, Alan C. Evans

MCGILL CENTRE FOR INTEGRATIVE NEUROSCIENCE, MCCONNELL BRAIN IMAGING CENTRE, MONTREAL NEUROLOGICAL INSTITUTE, MCGILL UNIVERSITY, MONTREAL, QUEBEC H3A 2B4, CANADA

NEUROIMAGE (2016),

HTTP://DX.DOI.ORG/10.1016/J.NEUROIMAGE.2016.03.062

Measuring Networks with: 1. DTI (Diffuse Tensor imaging)- employing FA

- Fractional anisotropy (FA) is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. FA is a measure often used in diffusion imaging where it is thought to reflect fiber density, axonal diameter, and myelination in white matter. The FA is an extension of the concept of eccentricity of conic sections in 3 dimensions, normalized to the unit range.

Measuring Networks with: 1. DTI (Diffuse Tensor imaging)-employing FA

- One common approach is the use of *DTI tractography* to delineate major white matter tracts, and compute measures such as FA (indicator of microstructural integrity) of the traced tracts at several developmental ages. The resulting age-related changes show the microstructural changes for the traced white matter tracts during development. In one such study, Lebel and Beaulieu used DTI based tractography and region of interest analyses on longitudinal scans of 103 healthy subjects aged 5–32 years (each volunteer scanned twice) to describe the exponential changes in the microstructural development of white matter (using FA) from childhood to adulthood (Lebel and Beaulieu, 2011).

Research findings indicate increasing integration and decreasing segregation of structural connectivity with age indicating network-level refinement mediated by white matter development.

Measuring Networks with: 2. rs-fMRI

- Resting state fMRI (rs-fMRI) is a functional imaging technique that permits measurement of spontaneous, low-frequency (0.1 Hz), and high-amplitude fluctuations while subjects are ‘at rest’ (not performing any overt task)
- Functional connectivity as assessed by the correlation of rs-fMRI signals has often been observed among functionally associated brain areas and is present even under anesthesia (Gusnard et al., 2001; Dosenbach et al., 2007; Fair et al., 2007, 2008; Greicius et al., 2009).
- Both ‘data-driven’ (e.g. independent component analysis (ICA)) and ‘hypothesis-based’ (a priori seed-selection) approaches have been used to investigate developmental changes in functional connectivity.

Measuring Networks with: 2. rs-fMRI

- On the other hand, hypothesis-based approach starts with a priori selected seed (brain region) with which functional connectivity is computed for the rest of the brain regions.
- Developmental trajectories from late childhood (8–12 years) through adolescence (13–17 years) to early adulthood (19–24 years) of 5 functionally distinct cingulate-based intrinsic connectivity networks (ICNs) -5 domains of self-regulatory control: i)motor control, ii) attentional/cognitive control, iii) conflict monitoring and error processing, iv) mentalizing and social processing, and v) emotional regulation.
- A pattern of diffuse local functional connectivity in children while more focal patterns of functional connectivity were seen in adults, consistent with developmental patterns of activation seen in functional neuroimaging studies that move from diffuse to more specific/focal patterns (Durston and Casey, 2006; Durston et al., 2006).

Pros and Cons to Traditional methods

- Pro: Both hypothesis-based (seed-based) and ICA approaches have proved very useful in studying specific networks or modules in detail.
- Con: Misses the bigger picture of how specific networks or modules interact with the remaining brain regions. This becomes especially relevant considering the fact that the coordinated activity within and across modules produces large-scale brain networks that are essential for efficient functioning of the brain
- E.g. studying a particular brain region, say, the anterior cingulate cortex (a seed region for the salience network) within the context of only the salience network will likely mask its function in default mode activity.

Pros and Cons- Example

Central Executive Network(Frontal Parietal) -key nodes

- dlPFC & PPC----memory and attention

Salience Network-key nodes

- frontal insular and dACC---detecting mapping internal and external events relevant to context. Connects w subcortical-limbic structures critical to reward and motivation

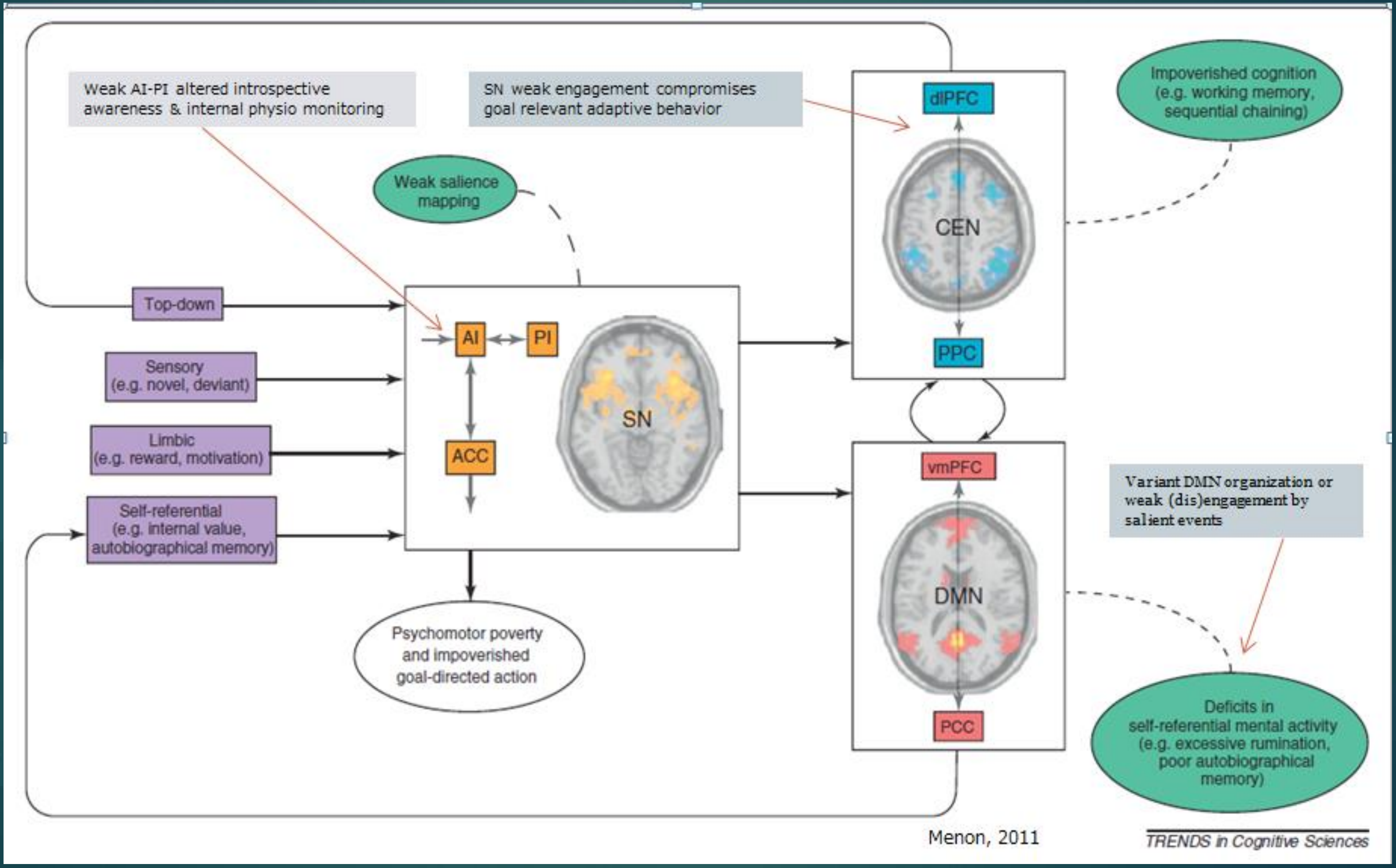
Cingulo-Opercular-key nodes

- dACC, ant insula, antPFC

DMN-key nodes

- PFC and PCC; self-referential, autobiographical, memory for scenario planning, moral decision making

Pros and Cons- Example



Graph-based connectivity

- The small-world behavior for a real network is ensured by checking for $Cp^{real}/Cp^{rand} > 1$ and $Lp^{real}/Lp^{rand} \sim 1$ where Cp^{rand} and Lp^{rand} are the mean clustering coefficient and characteristic path length of matched random networks which preserve the same number of nodes, edges, and degree distribution as the real network (Maslov and Sneppen, 2002; Rubinov and Sporns, 2010).

Graph-based connectivity

- Global efficiency (E_{global}) is a related measure, calculated as the average inverse characteristic path length (Latora and Marchiori, 2001). The use of global efficiency is more advantageous than the use of the characteristic path length particularly in the case of disconnected networks because disconnected nodes are considered to have infinite path length and correspondingly zero efficiency
- For a graph, a module is defined as the subset of nodes that are densely connected to each other and less so to nodes outside the module.

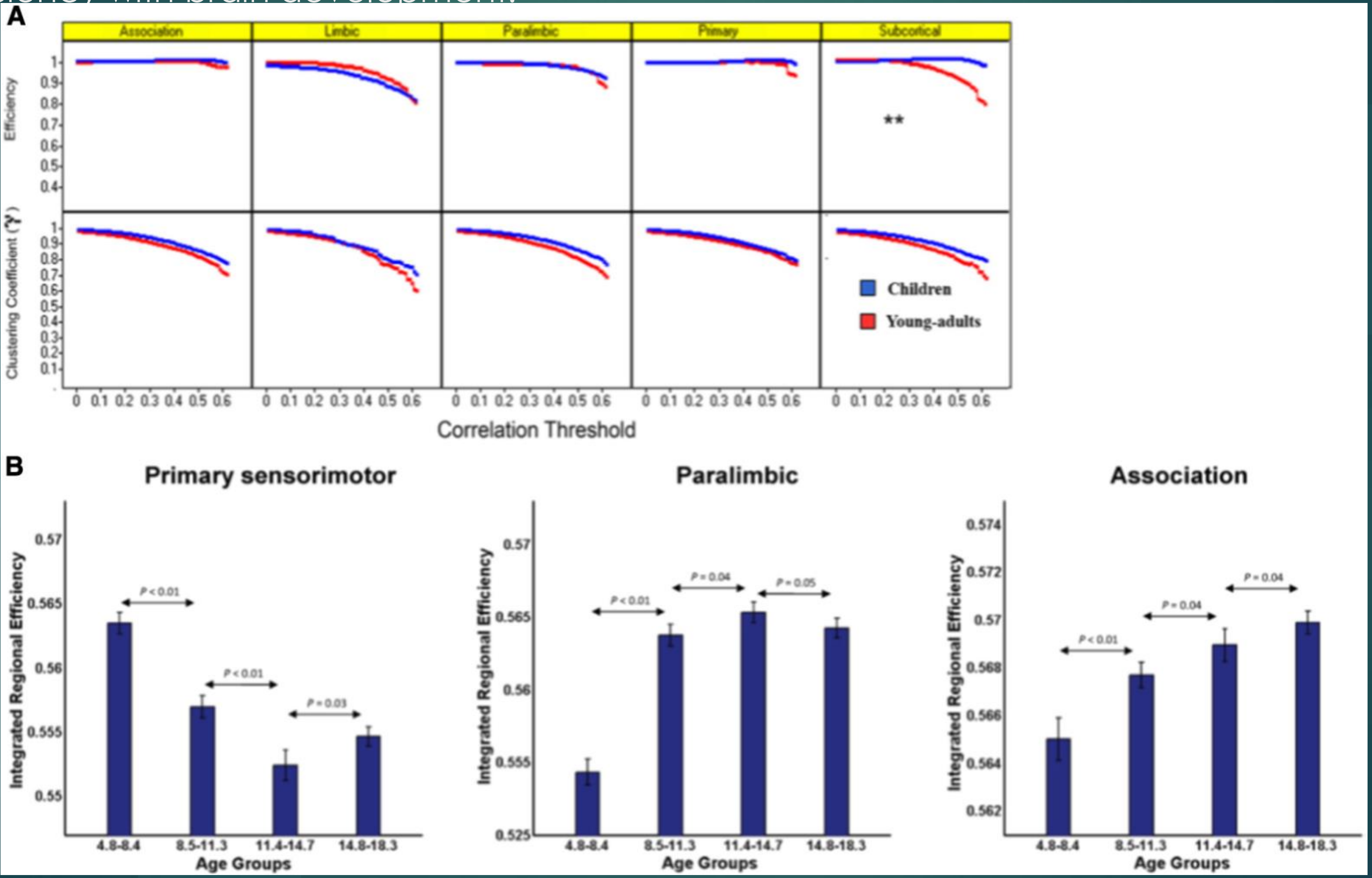
Graph-based connectivity: Developmental Studies

- There appears to be a developmental trajectory toward increased structural connectivity with development, consistent with white matter maturation.
- Graph-theoretic studies based on SCNs have revealed that brain networks in early development (1month) are stable exhibiting economic/optimal small world topology and non-random modular organization and show increased global efficiency and modularity in early development (Fan et al., 2011). Khundrakpam et al. (2013) showed that this stable organization continues in childhood and adolescence (Khundrakpam et al., 2013).

Graph-based connectivity: Developmental Studies

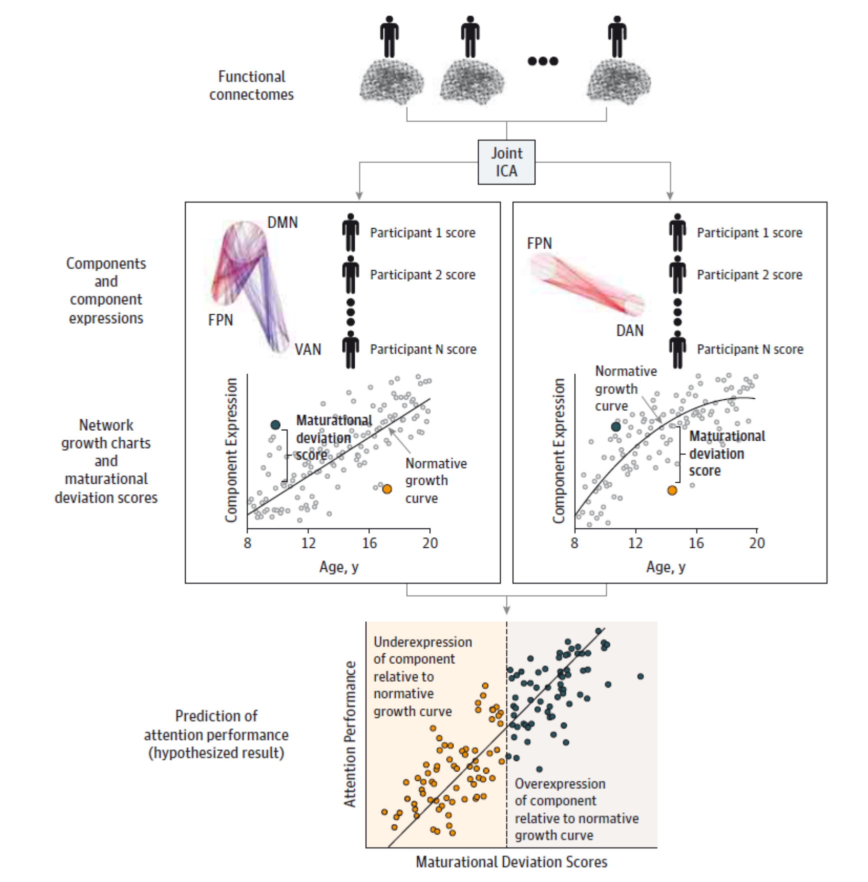
- During late childhood, prominent changes in global topological properties, specifically a significant reduction in local efficiency and modularity and increase in global efficiency, suggesting a shift of topological organization toward a more random configuration.
- The studies are confounded by:
  - fMRI studies used selected age ranges and selected brain regions
  - Comprehensive statistical comparisons were not performed for the global topological properties
  - Since these graph theoretic studies on development are from different imaging modalities that capture different tissue types and brain structures, different developmental trajectories of the global topological properties might be expected

Fig. 6. System-level topological changes with brain development. A. fMRI-based study showing efficiency of five major functional brain divisions (cortical and subcortical) in children and young adults (Supekar et al., 2009). Subcortical regions displayed prominent changes in efficiency between children and young adults. B. SCN-based study of regional efficiency of three major functional brain divisions (cortical regions only) (Khundrakpam et al., 2013). Primary sensorimotor regions displayed decreasing efficiency while paralimbic and higher-order association regions showed increasing efficiency with brain development.



Utilization of Connectivity in Clinical Disorders

Resting-state functional connectomes from 519 participants enter joint independent components analysis (ICA), which parses the connectomes into several cohesive components (2 illustrative components are shown in the boxes at middle). For each component, growth charts are then constructed that depict the normative change in component expression with age. Next, each participant is assigned a maturational deviation score for each component that reflects the degree to which that component is underexpressed or overexpressed relative to what is expected by age. These maturational deviation scores are then used as predictors of performance on a sustained attention task. DMN indicates default mode network; FPN, frontoparietal control network; VAN, ventral attention network.



Daniel Kessler, BS; Michael Angstadt, MAS; Chandra Sripada, MD, PhD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.0088
Published online April 13, 2016.

Genetic Factors

- Results from studies of these various developmental syndromes indicate that the mechanisms involved in the development of white matter tracts and connectivity are complex and not restricted simply to the guidance of axonal growth cones to their targets.
  - E.g. FOXG1B gene, which encodes a transcription factor that promotes the proliferation and inhibits the differentiation in cortical progenitor cells during the development of the telencephalon (Hanashima et al., 2004; Schell-Apacik et al., 2008).

Heredibility

- Disrupted functional connectivity in frontal lobe was associated with common genetic variants implicated in several neurodevelopmental disorders including autism (Scott-Van Zeeland et al., 2010).
- A study using longitudinal DTI data of 162 healthy adolescent twins and their siblings showed that the efficiency measures (global and local efficiency) of structural brain networks are highly heritable (Koenis et al., 2015)
- The efficiency measures increase during early adolescence relate to increase in intellectual abilities.

Conclusions from Developmental Connectivity

- 1. At the cellular level, synaptogenesis and synaptic pruning act as progressive and regressive forces, beginning in primary sensorimotor regions and later in anterior regions such as prefrontal cortex (Huttenlocher, 1990; Huttenlocher and Dabholkar, 1997), thus continuously shaping the formation and evolution of neural circuits.
- 2. In parallel to these synaptic level changes, brain structure and function also undergo progressive and regressive events (i.e., WM myelination and GM loss, respectively) at the macroscopic level, starting earliest at primary sensorimotor areas and occurring latest in higher-order association areas.
- 3. Intrinsic functional connectivity exhibits a shift from diffuse local functional connectivity in children to more focal patterns of functional connectivity in adults
- 4. The dynamic process of synaptogenesis and pruning that rewires connectivity at the neuronal level also operates at systems level helping to refine network connectivity in the developing brain.

Network Communication

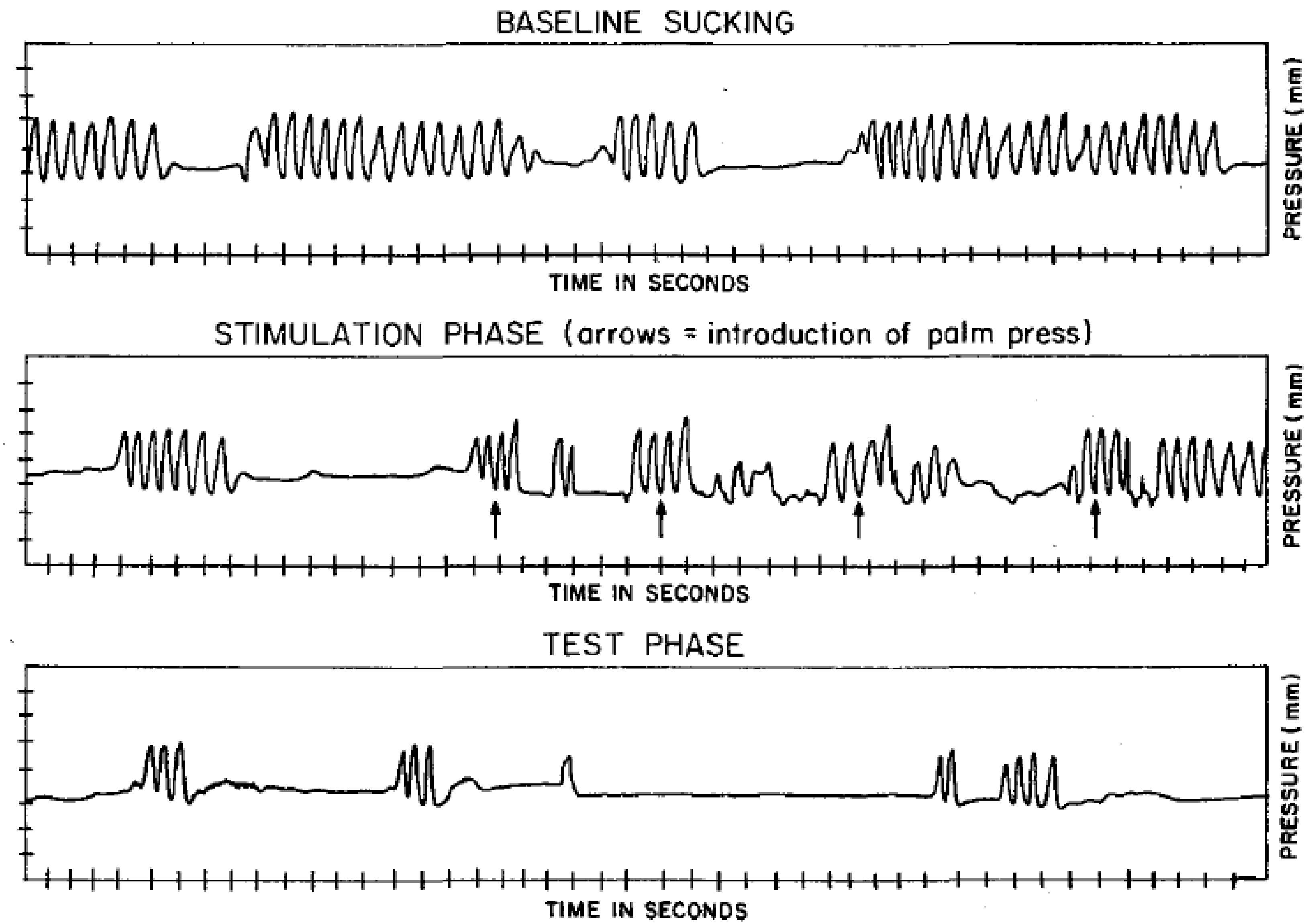
Communication within and Between Networks

- While the afore studies help to understand the "hard wiring" for structural networks facilitating communication in these networks, how is specific information encoded in these networks to direct information processing and adaptive responses – in other words - learning?

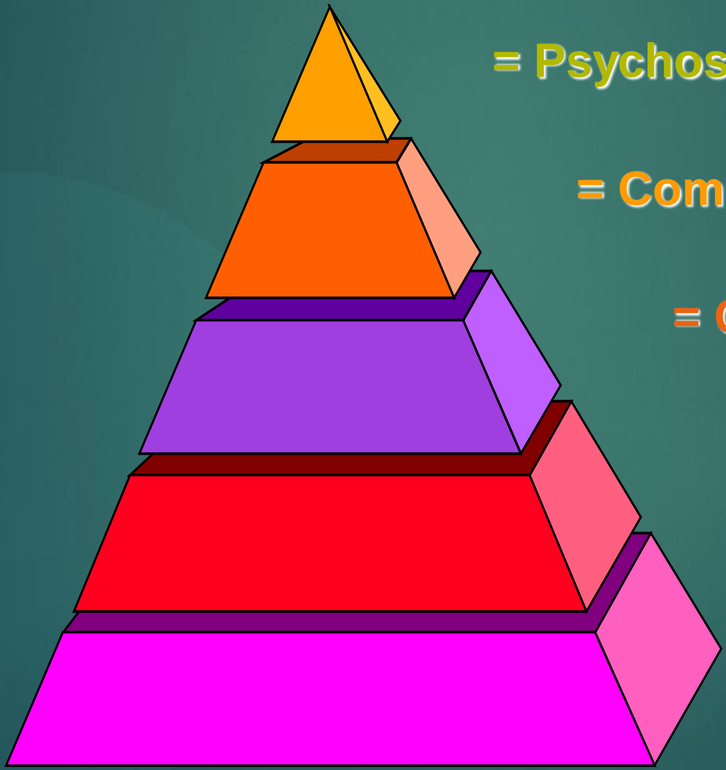
Is Learning “hard-wired”? Hierarchical development promotes more expansive “learning”

- Introduction of stimulation on a system trying “calibrate” or coordinate events in the ANS fundamentally limits adaptability by the CNS

  Ex: Newborn study – competing reflexes


BASELINE SUCKING
PRESSURE (mm)
TIME IN SECONDS
STIMULATION PHASE (arrows = introduction of palm press)
PRESSURE (mm)
TIME IN SECONDS
TEST PHASE
PRESSURE (mm)
TIME IN SECONDS

Functional Hierarchy of Functional System:



Definition

- Sensory Processing (Integration) Disorders refers to the body's way of handling and processing inputs from the environment
  - Jean Ayres, Ph.D. (Occupational Therapy) – Ayres, 1979.
  - Result of an aberrant developmental process
- Estimated to affect 5-16% of children and this can cause long-term impairment of intellectual and social development from disrupted processes attempting to integrated "high-bandwidth" information from multiple sensory modalities – Owen et al. ,2013
  - White matter problems
- Co-morbid with ADHD, ASD, and other pathologies BUT often exists in isolation (Ahn et al., 2004).

Communication: Backtracking from Experience

- Coordination of stimulus "perception" comes from time locked redundancies of stimulus events (classical conditioning) and the extent that responses to events lead to successful adaptive functioning (Operant conditioning)

What is defining temporal order in neural firing?

- Metabolic periodicity "coding"

Biological Rhythms- Cellular Processes

- Goodwin (1967) – continuous oscillations of cellular constituents establishes relative stable states of equilibrium despite minor fluctuation in environmental events.

- The production and depletion of metabolites serves to regulate synthesis of cellular proteins and the utilization of these proteins in a dynamic manner.
  - Not random but rather occur in patterns of non-linear oscillations and can be described by a set of differential equations.
  - These equations describe cellular volumetric shifts as function of the utilization curves of cellular proteins.
- The **time gradient** in these utilization curves describes the oscillatory mode of general cellular activity

- Negative feedback control loops play critical role in regulation of number of oscillations per unit time,,i.e. concentration of argenine, CTP, pyruvate, etc that spill out into intercellular space with certain periodicities establish temporal signals for neighboring cellular activity
  - The frequency and phase relations of these signals can establish a “code word” which would have specific effects on cells or axons receiving it.

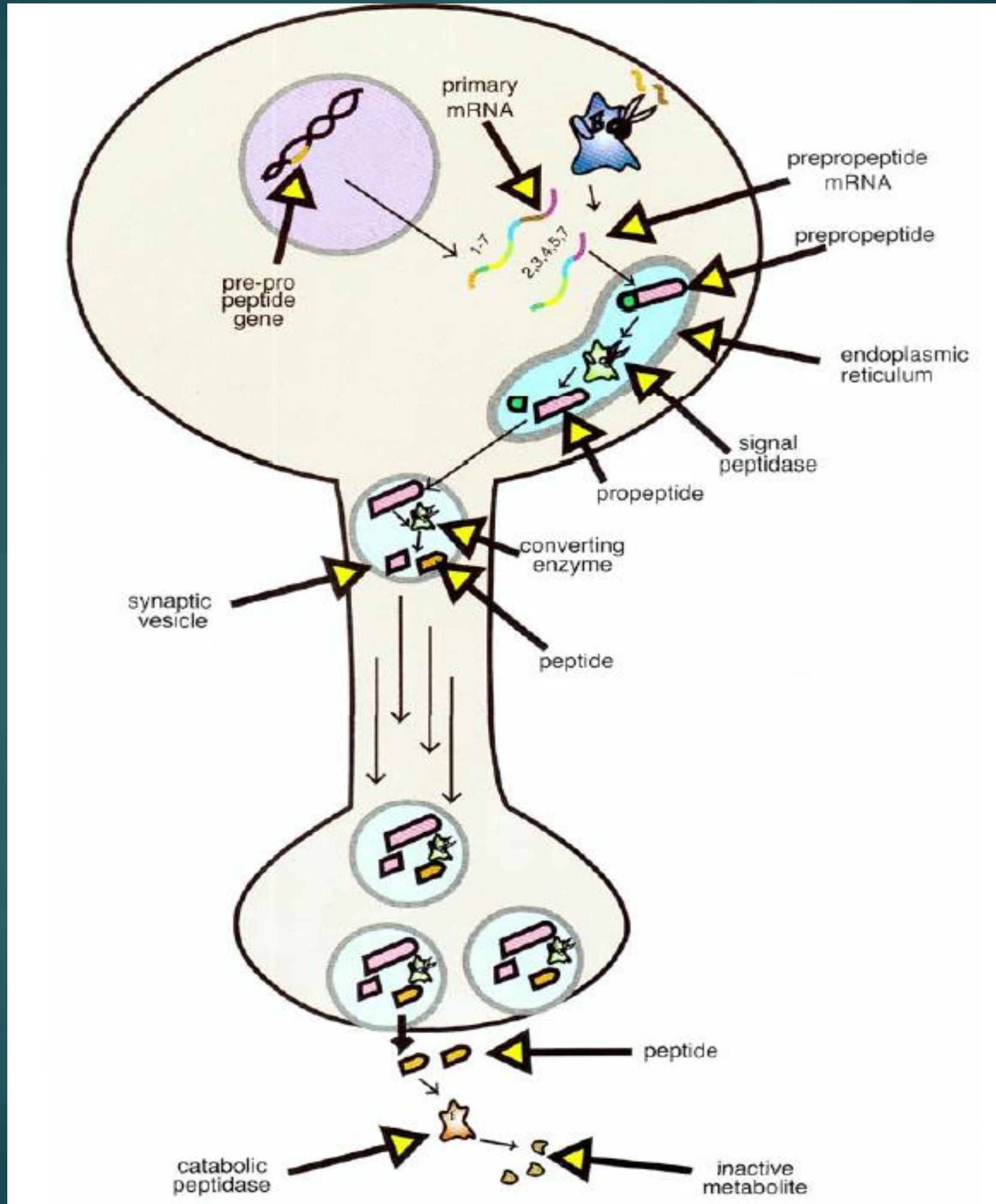
Cellular communication

- It has become apparent that the complex "biochemical" activities which underlie the structure and function of cells and organisms do not form a homogeneous pattern in time such that all processes occur simultaneously at fixed rates. Rather there is a rhythm to these activities whereby they are ordered relative to one another in time, first one and then another activity rising to a maximum and then falling off again.

Metabolic "Turnover" is the "rate" limiting factor

One of the major determinants of how rapidly steady states can be reached in the metabolic system, is the turnover rate of substrate molecules by the enzymes of intermediary metabolism. This falls largely in the range of 10-10"* molecules 'sec. (cf. Eigen and Hammes, 1963). The detailed studies of Chance and Hess (1959), Hess and Chance (1961), on changes in the pattern of glucose metabolism in ascites tumour cells following different disturbances show that very extensive changes in metabolic steady state occur in a matter of 1 or 2 min in response to large stimuli. For example, the level of glucose-6-phosphate rises from a very low value (~005 /LtM/g cells) to a new steady state value of about 0-8 /LiM/g cells in about 1 min after the addition of 7-5 mM of glucose to the system.

Time course for cellular processes to facilitate neural firing pre-determines firing rate

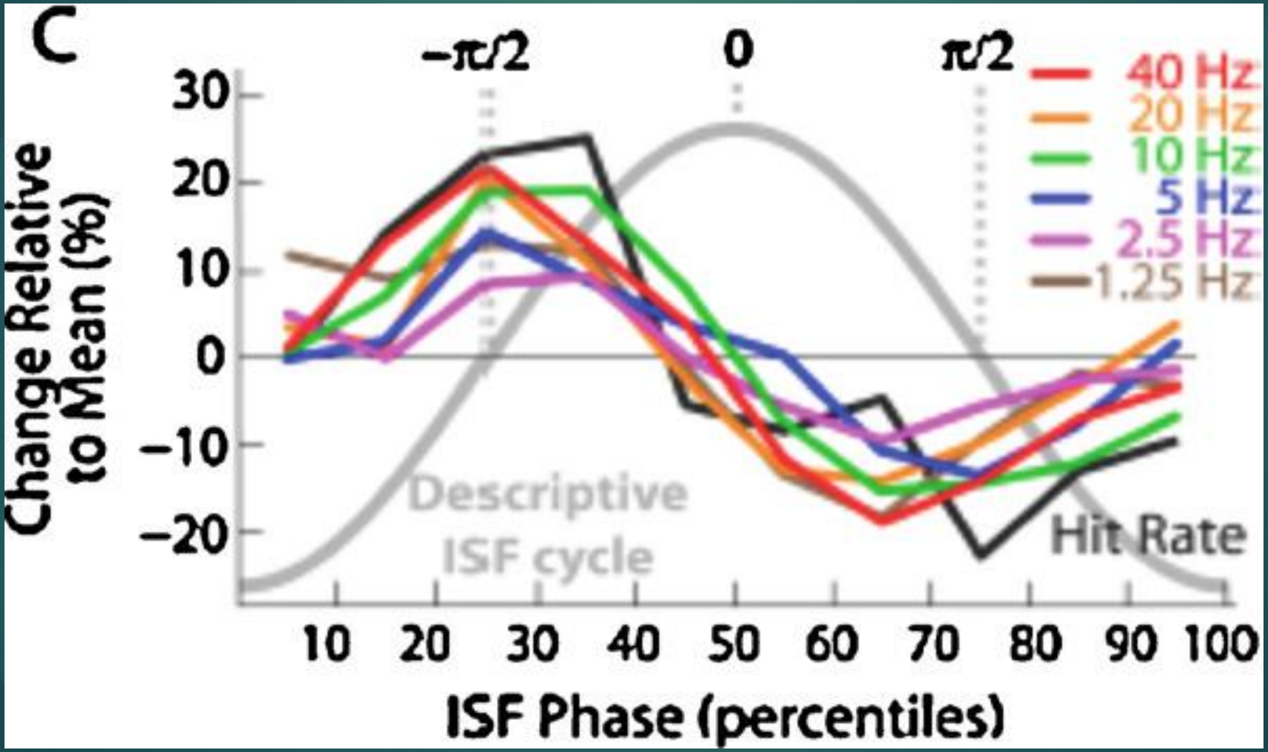


ahl, 2002

- Palva and Palva (2012)
  - have determined that the “Ultradian Rhythm” (< 0.01 hz) in EEG recordings, BOLD signals, neuronal activity levels, and behavioral time series are likely to image the same fundamental phenomenon; a ***superstructure*** of oscillatory ISFs that regulate both the excitatory level of functional networks and the integration between them.

- A complex communication "field" would be set up in terms of frequency, amplitude, and phase relationships among metabolic signals over a population of similar cells [or cells utilizing similar chemical components]

Coupling of higher-frequency oscillations to ISFs. In EEG recordings, amplitudes of 1–40 Hz oscillations (colored lines) modulate according to the phase of an ISF (0.01–0.1 Hz) and also mirror changes in behavioral performance (black line). ISFs inhabit a similar frequency range as that of the fluctuating BOLD signal, suggesting the latter may bear a similar phase-relationship to higher frequency oscillations and behavioral performance. Reproduced with permission from Monto et al. (2008). ISF, infra-slow fluctuation.



Taken from Meehan et. al, 2012

Mesoscale infraslow spontaneous membrane potential fluctuations recapitulate high-frequency activity cortical motifs

Allen W. Chan, Majid H. Mohajerani, Jeffrey M. LeDue, Yu Tian Wang & Timothy H. Murphy

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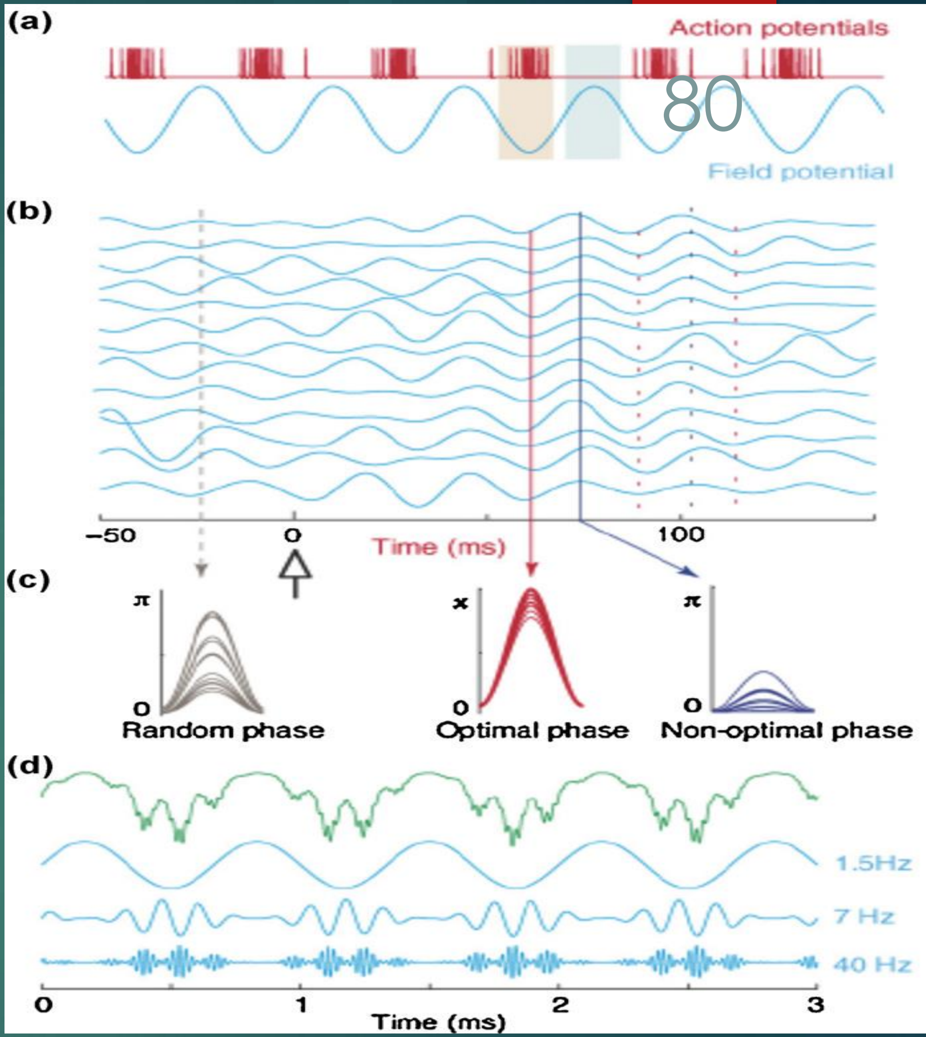
Abstract

Neuroimaging of spontaneous, resting-state infraslow (<0.1 Hz) brain activity has been used to reveal the regional functional organization of the brain and may lead to the identification of novel biomarkers of neurological disease. However, these imaging studies generally rely on indirect measures of neuronal activity and the nature of the neuronal activity correlate remains unclear. Here we show, using wide-field, voltage-sensitive dye imaging, the mesoscale spatiotemporal structure and pharmacological dependence of spontaneous, infraslow cortical activity in anaesthetized and awake mice. Spontaneous infraslow activity is regionally distinct, correlates with electroencephalography and local field potential recordings, and shows bilateral symmetry between cortical hemispheres. Infraslow activity is attenuated and its functional structure abolished after treatment with voltage-gated sodium channel and glutamate receptor antagonists. Correlation analysis reveals patterns of infraslow regional connectivity that are analogous to cortical motifs observed from higher-frequency spontaneous activity and reflect the underlying framework of intracortical axonal projections.

- Kandel & Schwartz (1982) – changes in neural cells underlie the basis of learning and memory:
  - The learning/memory of an event resides in the **time course** of the chemical processes utilized in facilitating the events juxtaposed on other ongoing cyclical events

- Varela, John and Schwartz (1978) noted that photic stimulation differentially phase locked to the alpha rhythm determined the perception of two contiguous flashes as one flash, one light in motion, or as two successive light flashes.
  - Background alpha serves as “temporal template” . A significant correlation between percent alpha or frequencies which were harmonic or sub-harmonic in alpha as noted in EEG and the accuracy of time related tasks.

Proposed relationship between oscillatory phase, neuronal excitability, and stimulus events. (A) A putative relationship between LFP phase of a local neuronal population and action potential firing rate, which here is high during optimal and low during non-optimal phases. (B) When superimposed, traces from single trials show random ambient phases, which reset and align following a stimulus presentation (time zero, arrow). (C) Response amplitudes to sensory events are highly variable during the pre-stimulus period, are enhanced during optimal phase, and are suppressed during non-optimal phase. (D) A stereotypical complex waveform, when broken into its component frequencies, reveals low-frequency phase modulation of higher-frequency oscillation amplitude, or phase-amplitude coupling, in a nested fashion. Reproduced with permission from Schroeder et al. (2008). LFP, local field potential.



Taken from: Neurocognitive networks: Findings, models, and theory Timothy P. Meehan, Steven L. Bressler, 2012.

Adaptability is achieved by temporal coupling in networks underlying harmonics

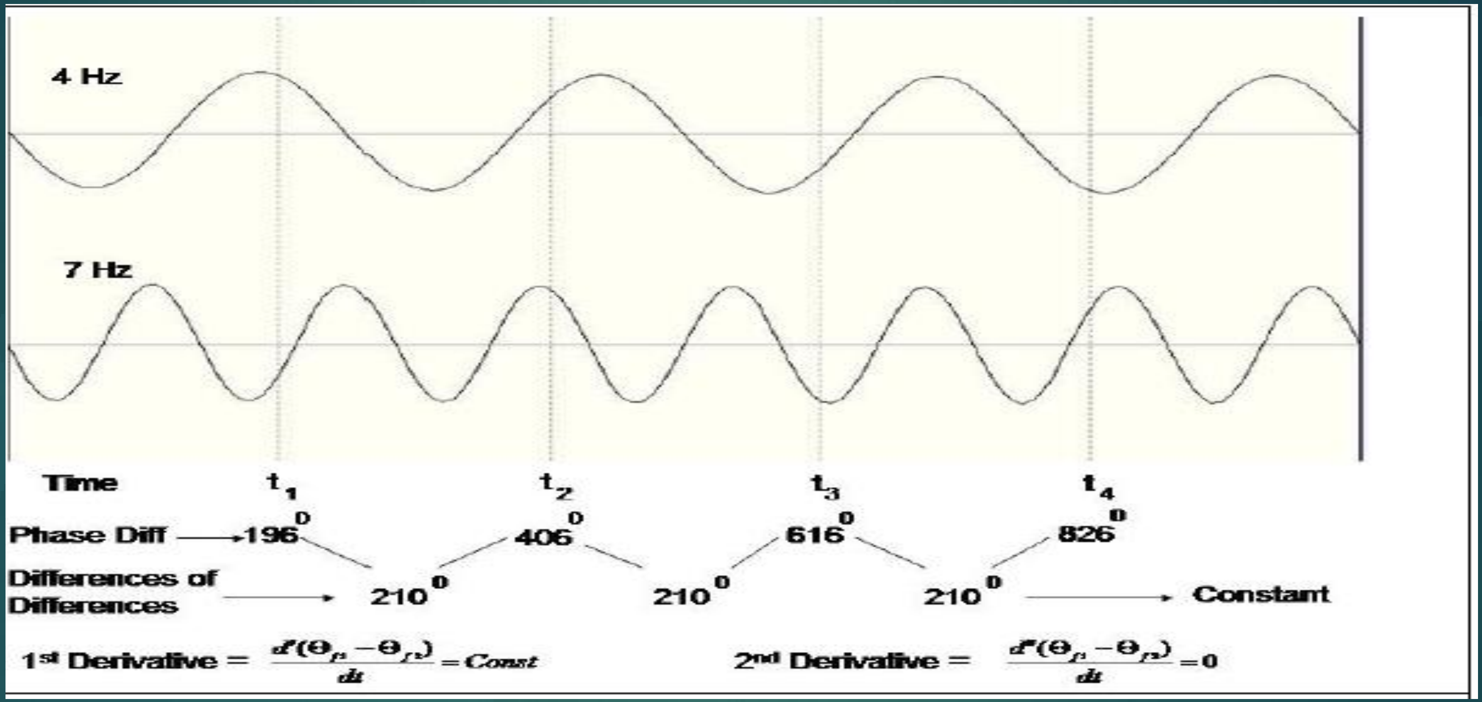
Meehan et al., 2012

- Yet, they are unstable with respect to other directions, and thus the system is capable of leaving the vicinity of one metastable state along these directions and moving to another one. The trajectories followed by these state transitions are known as *transients*.

Meehan et al., 2012

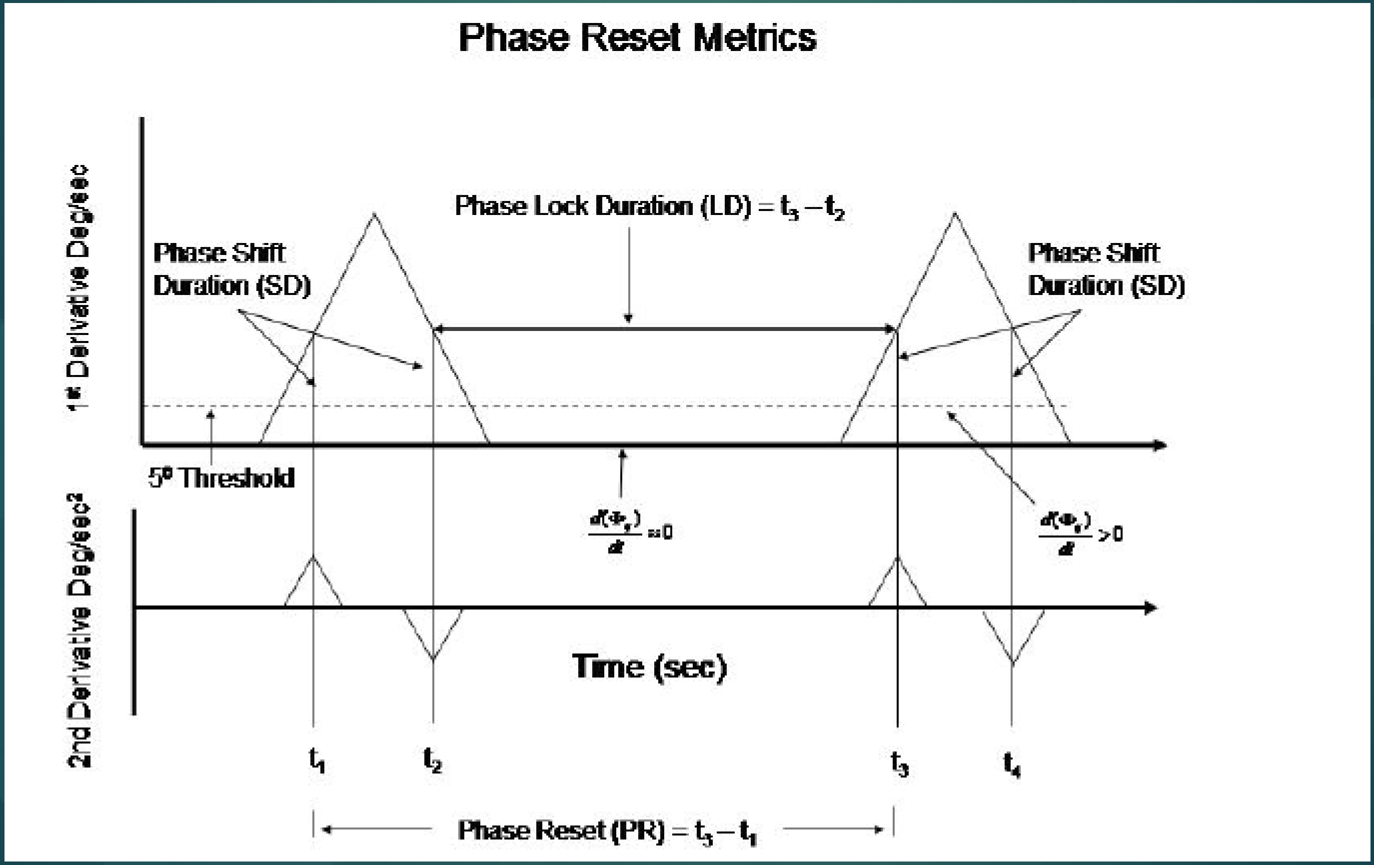
- Beta and gamma oscillations appear to have different functional capabilities in cortex. The switch from co-existent gamma and beta2 to global beta1 oscillations implies that the cortex is able to: (1) manifest ***temporal memory*** as ongoing beta oscillations; (2) engage in long-distance coordination by phase synchronization of those oscillations across cortical regions; and (3) bind multimodal features by interregional phase synchronization without competition between inputs (Kopell, 2010). Since experimental evidence shows that beta oscillatory phase synchronization is involved in cognitive functions such as visual short-term memory (Tallon-Baudry et al., 2001), sentence comprehension (Weiss et al., 2005), and sensory-motor integration (Lalo et al., 2007), these functions appear to be dependent on the dynamic properties of cortical cell assemblies, which may represent the nodes of neurocognitive networks.

Connection Basics –Phase Couplings



Cross frequency PR uses same model; when 2nd derivative between two oscillators =0, then in PL

Connection Basics – Developmental, Phase Reset



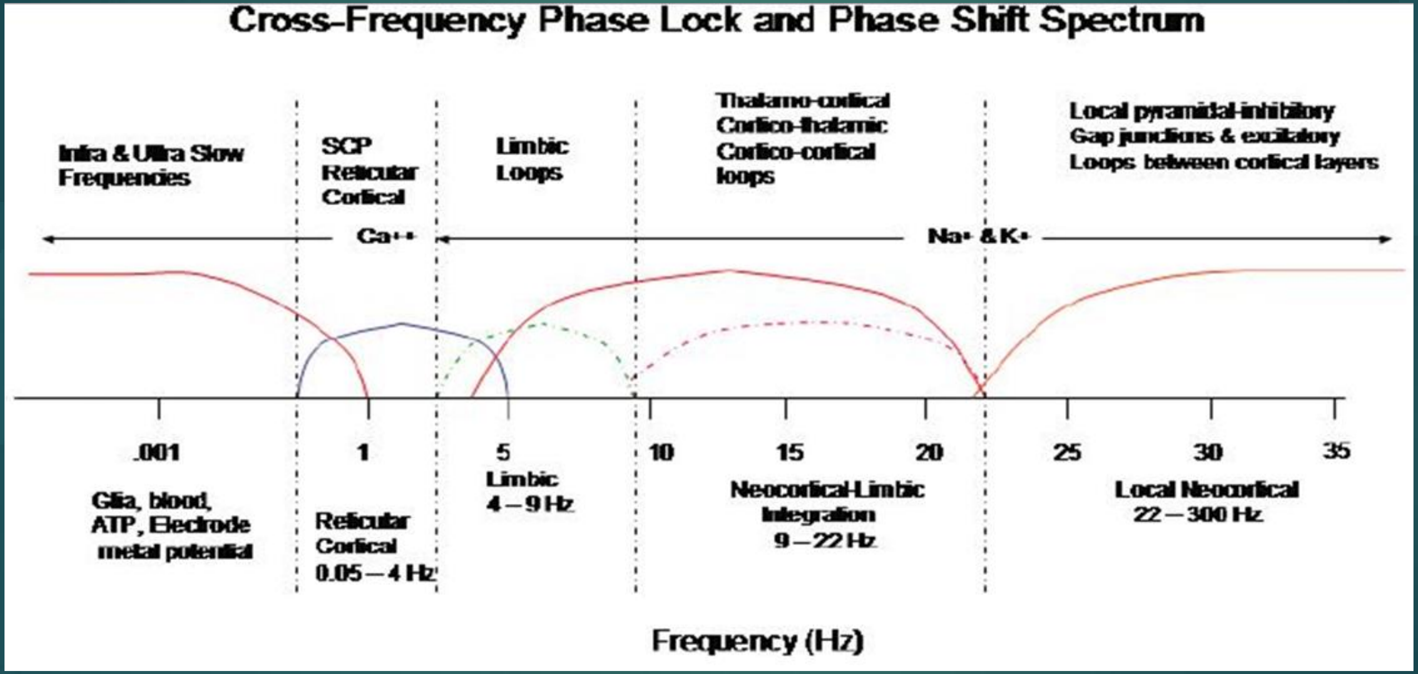
PSD & PLD-Perceptual Frame

- To distinguish events successive in time need 40 ms-auditory & 140 ms for visual stimuli, (Varela,1995).
- Learning from discontinuous sequence of narrow time windows.
- PSD & PLD are on going related to external events or background emergent process of approx. 40-80 sec (uncertainty/chaos) PSD, 150- 800ms (certainty/stability)PLD

PSD & PLD-Perceptual Frame

- During phase reset large assemblies of neurons may be in a simulated "refractory" period because locked neurons are not available for reallocation called by a different cluster.
- When PLD occurs over long distance it reduces the size of the cluster of idling neurons- synchronous high amplitude.
- Seen when stimulus lock PR causes Event Related Desynchronization (Klimesh,2007) ie spatially distributed/differentiated micro binding= < idling neurons,= less amplitude post stimulus.

Connection Basics



Thatcher, 2015

Fig. 1.2.3-12 Illustration of the 1/f nesting of high frequencies inside of low frequencies with different rhythm sources. Cross-frequency synchrony includes neocortical local rhythms phase locked with limbic and slow reticular-cortical rhythms and thalamic rhythms. The infra or ultra-slow frequency range (approx. 0.01 Hz to 0.001 Hz) is dominated by non-neural sources, the slow-cortical frequency range and the delta frequency range (approx. .05 Hz to 4 Hz) are primarily cortical in origin with reticular formation modulation, the theta frequency range (approx. 4 Hz to 9 Hz) is a mixture of hypothalamic-septo-hippocampal pacemakers and local circuits as well as thalamo-cortical and cortico-cortical oscillations; the alpha and beta frequency range (approx. 9 Hz to 22 Hz) involves thalamo-cortical, cortico-thalamic and cortico-cortical oscillations and the gamma and high gamma frequency range (approx. 22 Hz to 300 Hz) is mediated primarily by local cortical loops involving GABA and Gap junction local inhibition and excitation). (Thatcher, 2015)

Connection Basics – Developmental, Phase Reset

- Phase reset is comprised of phase shift duration (PSD) and phase lock duration (PLD)
- PSD is a period of instability, due to minimally coupled oscillators, on the edge of chaos/collapse.
- PSD allows for an energy free release of existing (cross)frequency couplings within and between areas, and a call out to available neuronal resources.
- Longer PSDs associated w higher I.Q. (recruitment of sufficient neuronal resources for processing); shorter PSDs - insufficient resources proposed to account for perseveration in such disorders as autism.

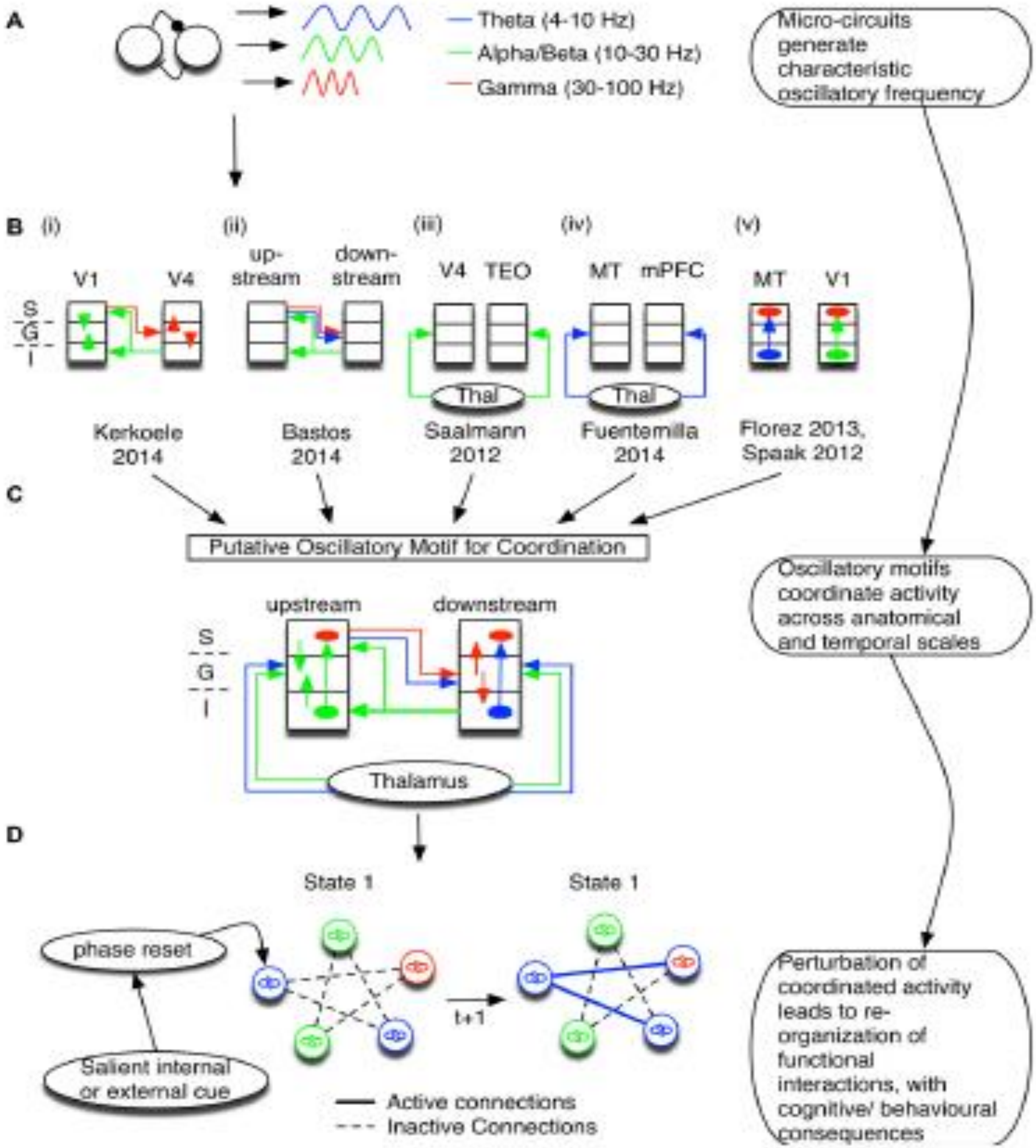
Connection Basics – Developmental, Phase Reset

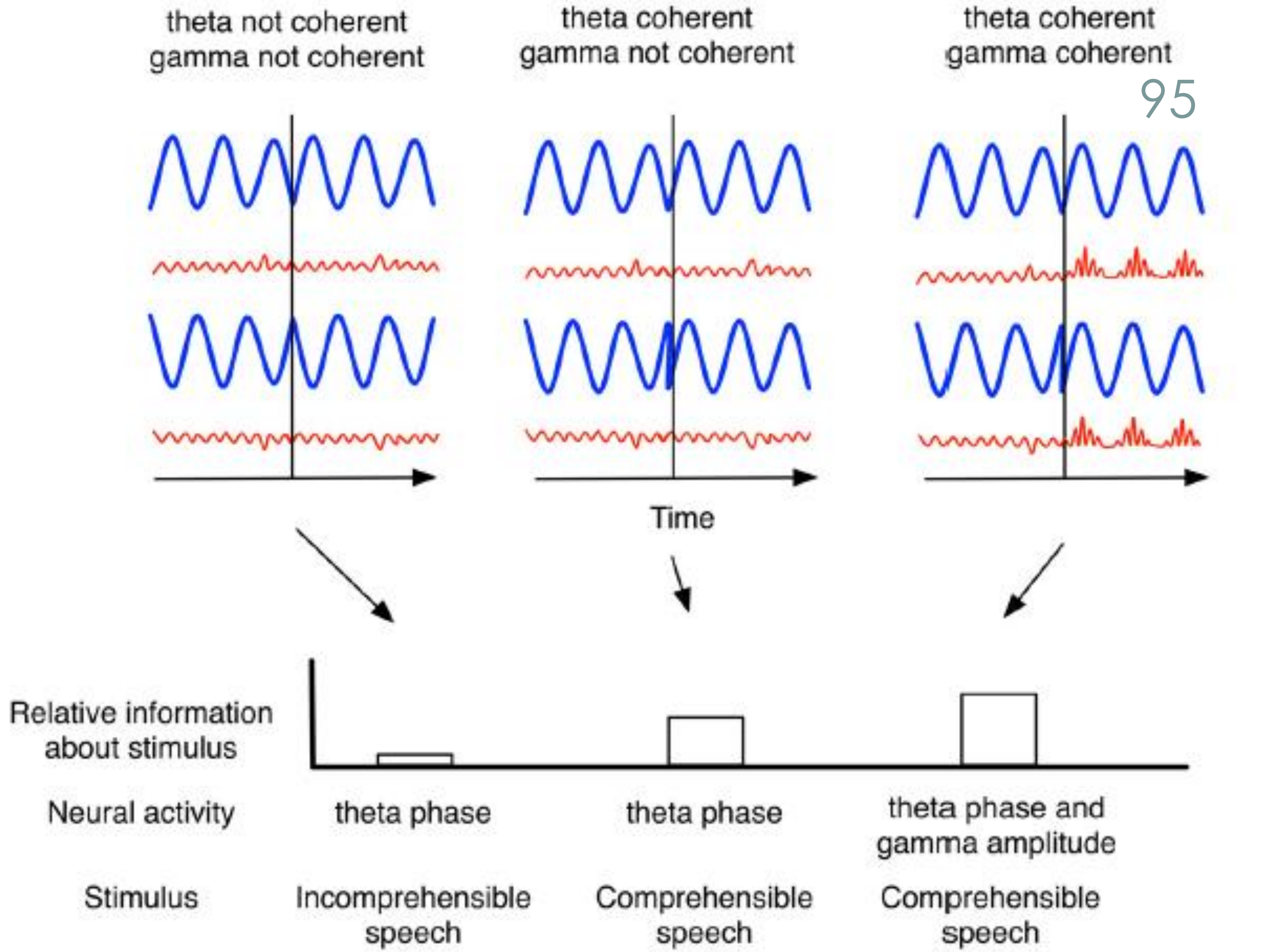
- Phase lock duration (PLD), a time period of stability-the binding of neuronal units within and across frequencies for information processing.
- Shorter PLD intervals associated with higher I.Q.; long PLD intervals associated with less efficient processing.
- High correlation between PLD and Coherence because COH is the consistency of phase relationships which contributes to stability.
- Inverse relationship between PSD & PLD; low R2

A Role of Phase-Resetting in Coordinating Large Scale Neural Networks During Attention and Goal-Directed Behavior *Benjamin Voloh and Thilo Womelsdorf**

REVIEW PUBLISHED: 08 MARCH 2016 DOI: 10.3389/FNSYS.2016.00018

- Short periods of oscillatory activation are ubiquitous signatures of neural circuits. A broad range of studies documents not only their circuit origins, but also a fundamental role for oscillatory activity in coordinating information transfer during goal directed behavior. Recent studies suggest that resetting the phase of ongoing oscillatory activity to endogenous or exogenous cues facilitates coordinated information transfer within circuits and between distributed brain areas. Phase resets: (1) set a "neural context" in terms of ***narrow band frequencies*** that uniquely characterizes the activated circuits; (2) impose coherent low frequency phases to which high frequency activations ***can synchronize***, identifiable as cross-frequency correlations across large anatomical distances; (3) are critical for neural coding models that depend on phase, increasing the **informational content** of neural representations; and (4) likely originate from the dynamics of canonical E-I circuits that are anatomically ubiquitous. These multiple signatures of phase resets are directly linked to enhanced **information transfer and behavioral success**. Phase resets re-organize oscillations in diverse task contexts, including sensory perception, attentional stimulus selection, cross-modal integration, Pavlovian conditioning, and spatial navigation.

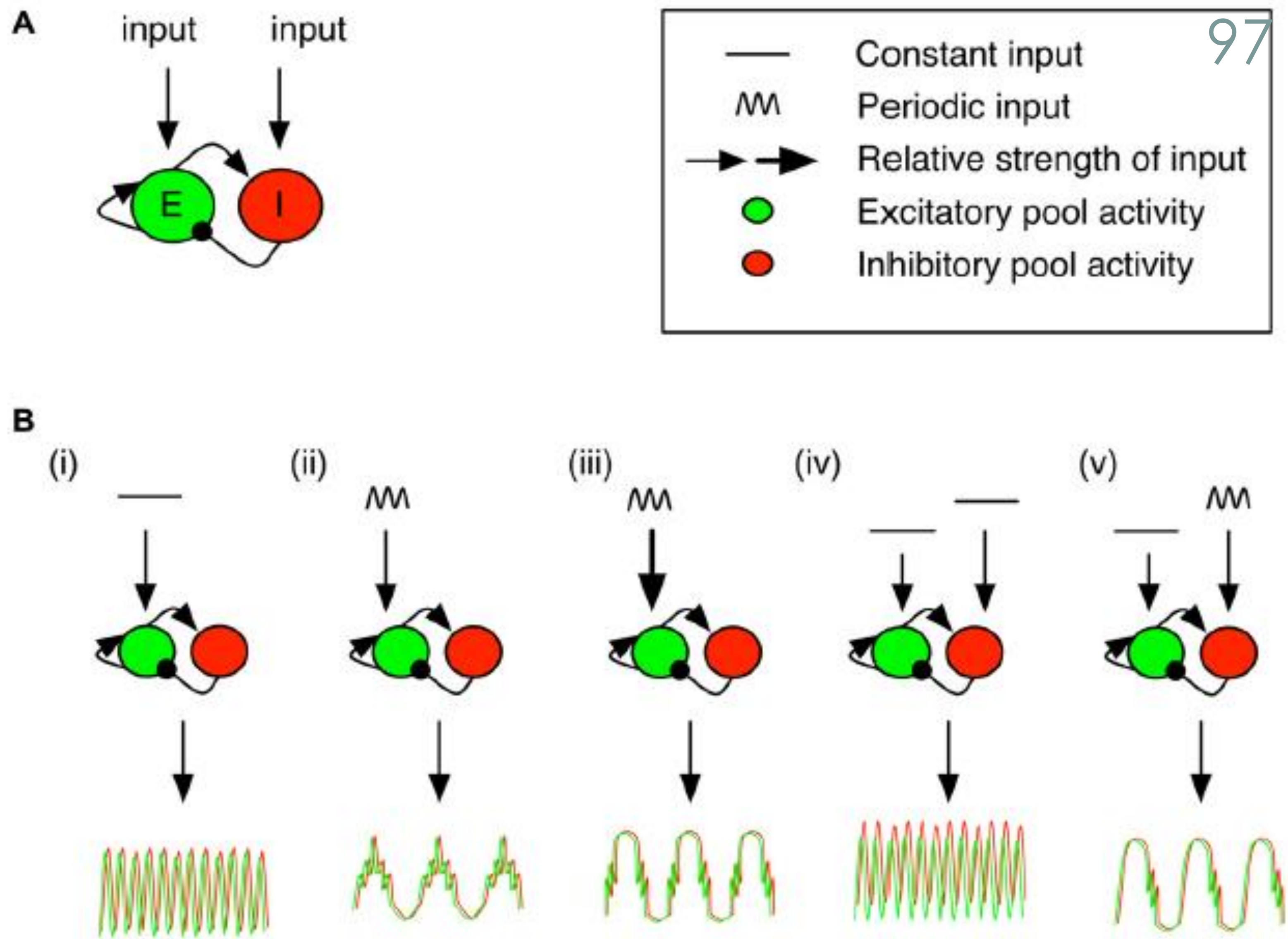

A
Theta (4-10 Hz)
Alpha/Beta (10-30 Hz)
Gamma (30-100 Hz)
Micro-circuits generate characteristic oscillatory frequency
B (i)
(ii)
(iii)
(iv)
(v)
V1
V4
up-stream
down-stream
V4
TEO
MT
mPFC
MT
V1
S
G
I
Thal
Thal
Kerkoele 2014
Bastos 2014
Saalmann 2012
Fuentemilla 2014
Florez 2013, Spaak 2012
C
Putative Oscillatory Motif for Coordination
upstream
downstream
S
G
I
Thalamus
Oscillatory motifs coordinate activity across anatomical and temporal scales
D
State 1
State 1
phase reset
Salient internal or external cue
t+1
Active connections
Inactive Connections
Perturbation of coordinated activity leads to re-organization of functional interactions, with cognitive/ behavioural consequences



theta not coherent
gamma not coherent
theta coherent
gamma not coherent
theta coherent
gamma coherent
Time
Relative information about stimulus
Neural activity
theta phase
theta phase
theta phase and gamma amplitude
Stimulus
Incomprehensible speech
Comprehensible speech
Comprehensible speech

Example: Language Development

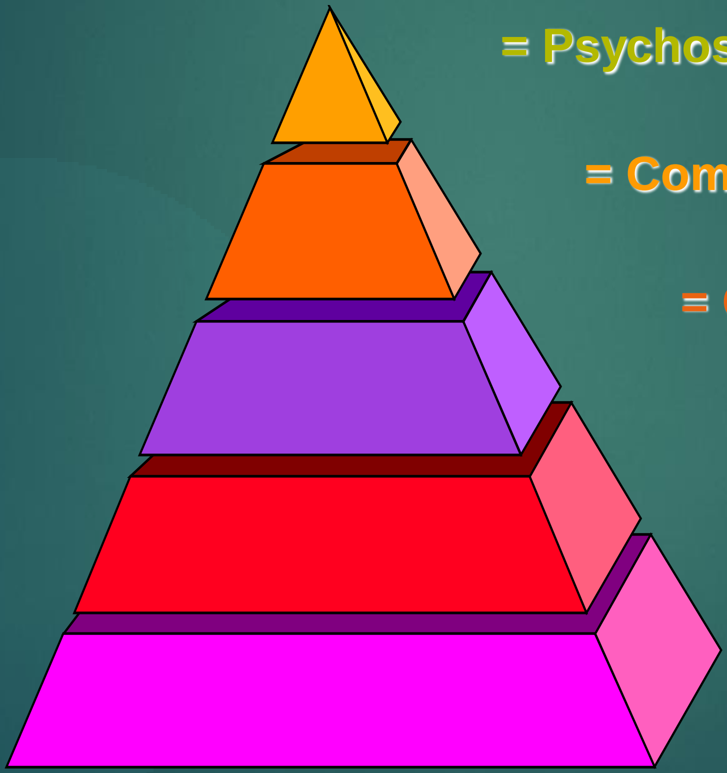
- 1. Reproducing sounds (sound over time only)
- 2. Reproducing words (complex sounds over time only)
- 3. Reproducing phrases (series of complex sounds without context)
- 4. Utilizing phrases in the right "contexts" – now communication
- 5. Applying phrases to generalize across contexts – higher order – adolescent language- creating a "new language"


A
input
input
E
I
Constant input
Periodic input
Relative strength of input
Excitatory pool activity
Inhibitory pool activity
B
(i)
(ii)
(iii)
(iv)
(v)

Building Network Clusters

- Emergence from perceptual/emotional networks to memory networks which provide frames of references which enable response networks as part of the decision making process (all of this happens in milliseconds – precognition?).

Cognition (Schemas)



= Psychosocial /Occupational Success

= Communication/Independent Care

= Cognition/Physical Mngmnt

= Sensory/Perceptual

= Historical (Genetic)
+ Neural

Meehan et al., 2012

- Neurocognitive networks may have a nested structure, whereby nodes contain levels of complexity at progressively more microscopic scales, and processes at all these lower levels may contribute to function at the macroscopic scale.

Connection Basics

Cross-Frequency Rich Club (0.5 Hz – 8 Hz), Feeder Hubs (8 – 20Hz) & Peripheral Hubs (> 20 hz)

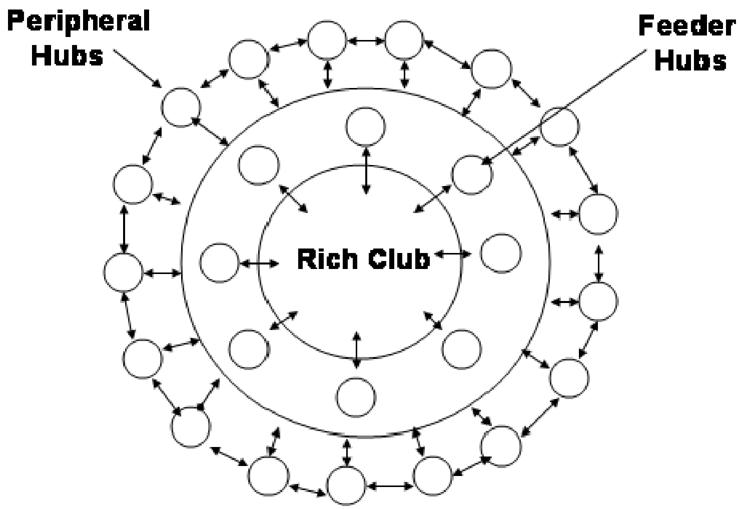


Fig. 5.0-2 Illustration of the Gallo et al (2015) Rich Club cross-frequency model where the core lower frequency and high density rich club mediates mood, anxiety and motivation that is surrounded by higher frequency hubs that connect to the central core rich club and the surrounding peripheral hubs that that do not directly connect to the rich club oscillate at higher frequencies (> 20 Hz) and mediate high speed information processing in sensory networks.

Thatcher, 2015

Recognizing sensory/temporal redundancies is the root of perception and learning

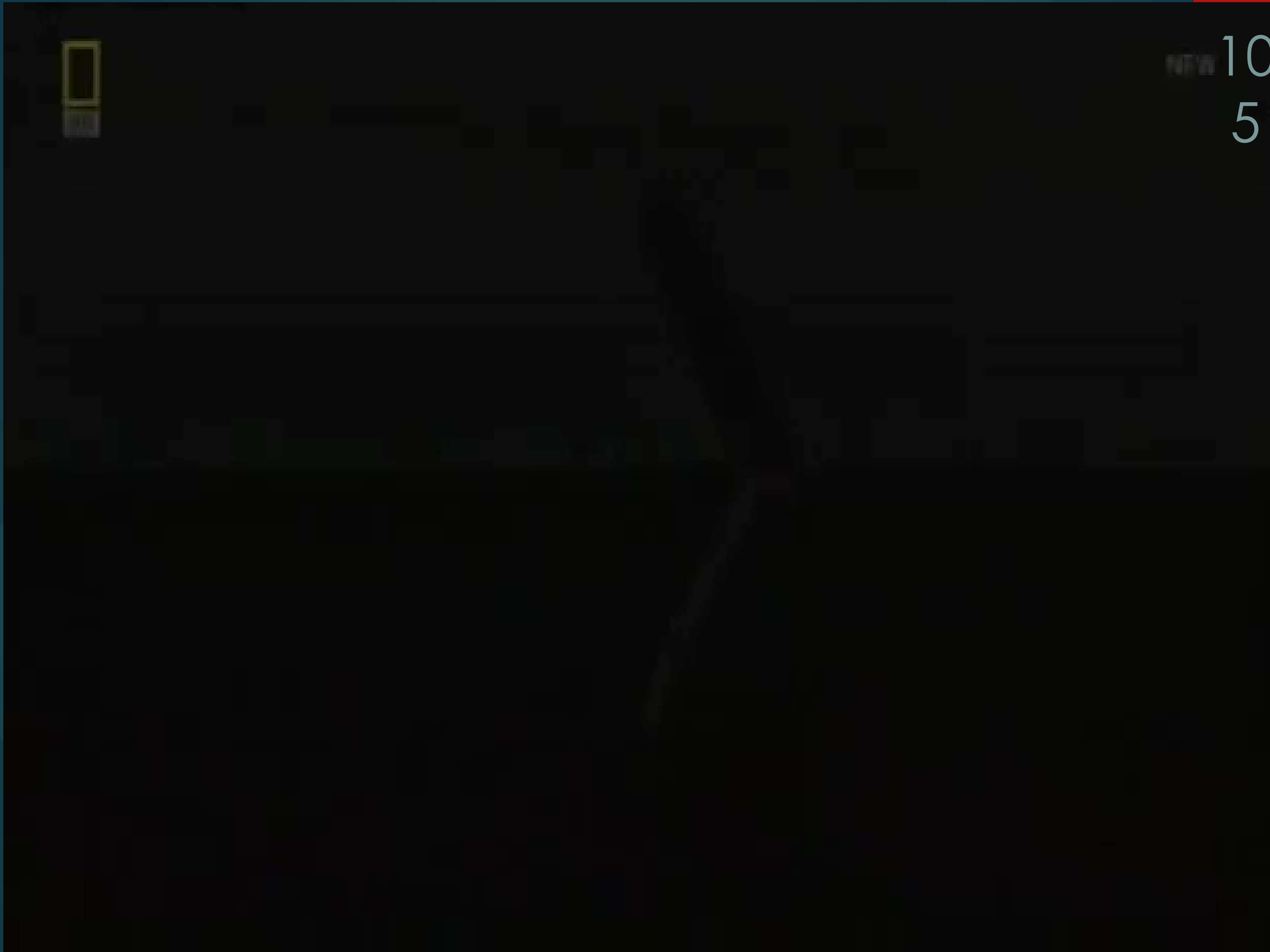
- The redundancy of two events in time allows us to "associate" the events and allows us to incorporate this association into or world of schemas or knowledge. When the associated events are responses themselves and these responses "compete" the system must either accommodate them adaptively or if non-adaptive response cannot be realized – we experience distress

Sensory- Perceptual Schemas

- The system first develops network “schemas” by the type of experiences we have in the real world impinging on the neural system over and over again so these neural systems “learn” to have expectancies of how the world should work.

Neuroception

(FROM STEPHEN PORGES)



Piagetian Concepts

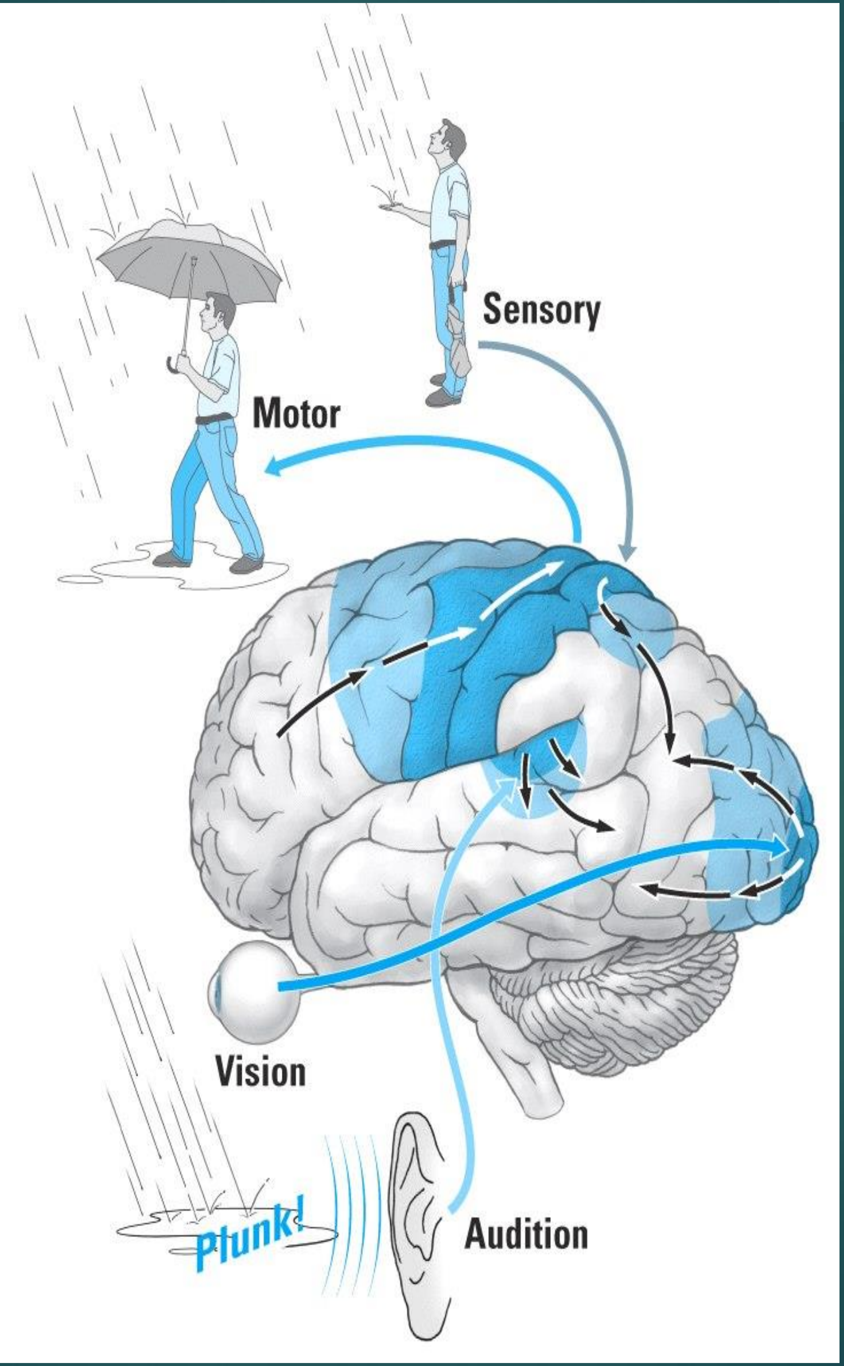
- **Assimilation** is a process that manages how we take in **new information** and incorporate that new information into our **existing knowledge**.
- Piaget used the term **schema** to refer to a category of knowledge that you currently hold that helps you understand the world you live in and provides some basic guidance for future events. A schema describes how we organize information. We store information as a particular schema until it is needed.
- The process of **accommodation** involves altering one's existing schemas, or ideas, as a result of new information or new experiences. New schemas may also be developed during this process.

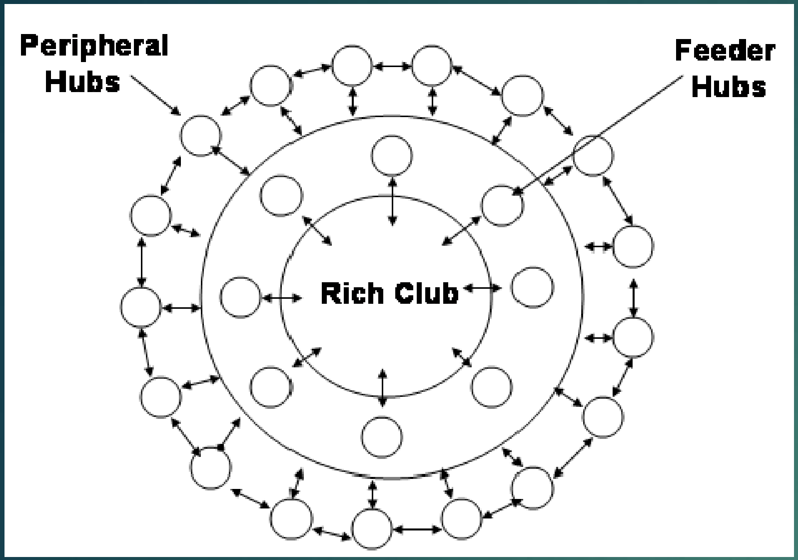
Higher Ordered Developmental Shift

- Networks the define and coordinate "perceptual" organization and thereby define cognitive "sets" give way to enable using learned concepts and abstractions to "over-rule" network neuro-caption as a decision making process about how the world works and how to respond in such a world.

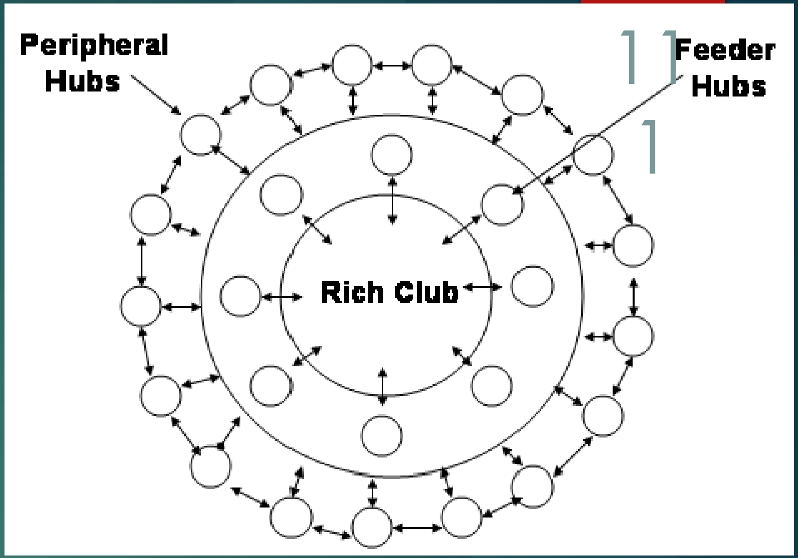
- This facilitates alternative response thinking – executive functioning – problem solve

Piagetian Development

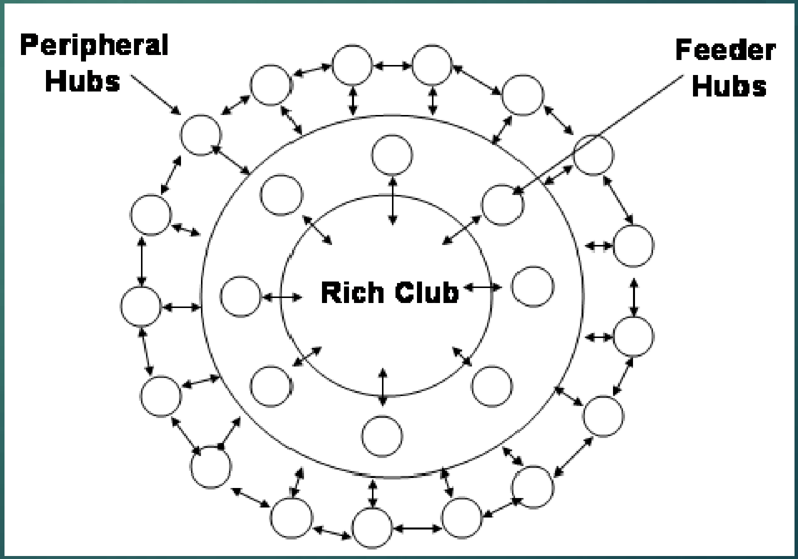

Sensory
Motor
Vision
Plunk!
Audition



Level I – Perceptual/Emotional



Level II – Memory Matching - Assimilation



Level III- Decision Making Response/Accommodation

Final Conclusions

- There are definitively structure-function relationships that evolve into networks optimizing adaptability and "survivability"
- While methods describing the development of gray matter and white matter in the human brain have been useful, the details of "temporal coding" and directionality within and across networks is still in infancy.
- The ability to refine optimized interventions is confounded by dynamic nature across age and across individuals including factors of metabolic variance due to dietary/chemical intrusions

Final Conclusions (2)

- Behavior adaptation and response is a result of our histories and experiences represented in nested networks
- ALL of our constructs are a function of the brain
- We define our reality by experiencing things in context- we have expectations
- We "feel" things that also based on these expectations
- Common Experiences result in common behaviors and ways we come to expect how people will respond and react to a given situation – acceptable "social" behavior

Problem for EEG Neurofeedback Therapy Protocols:

- The structure-function landscape keeps changing in course of development when training a specific structure-function relationship in a child, we may be assuming certain maturational "states" of these networks that simply do not exist
- If genetics plays a significant role in developmental connections at a given age and the "efficiency" of these networks, what are the "limits" in an individual to which we can expect to alter these intrinsic networks and their efficiency
- An important limitation of the available fMRI studies is that hemodynamic signals only provide an indirect measure of neuronal activity. In the contrast, electroencephalography (EEG) directly measures electrophysiological activity of the brain. Little is known about the brain-wide organization of such spontaneous neuronal population signals at resting state. It is not entirely clear if or how the network structure built upon slowly fluctuating hemodynamic signals is represented in terms of fast, dynamic and spontaneous neuronal activity.