Multi-level explanations in neuroscience: from genes to subjective experiences. II

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Cracow School of Theoretical Physics, LVIII Course, Zakopane, 15-23 June,
Neuroscience: Machine Learning Meets Fundamental Theory

On the threshold of a dream …

From mind to AI to NN to multi-level phenomics.

Part I: Brain and ML inspirations.

Brain ⇔ Mind relations, phenomics, **RDoC**.

Part II: Neurodynamics.

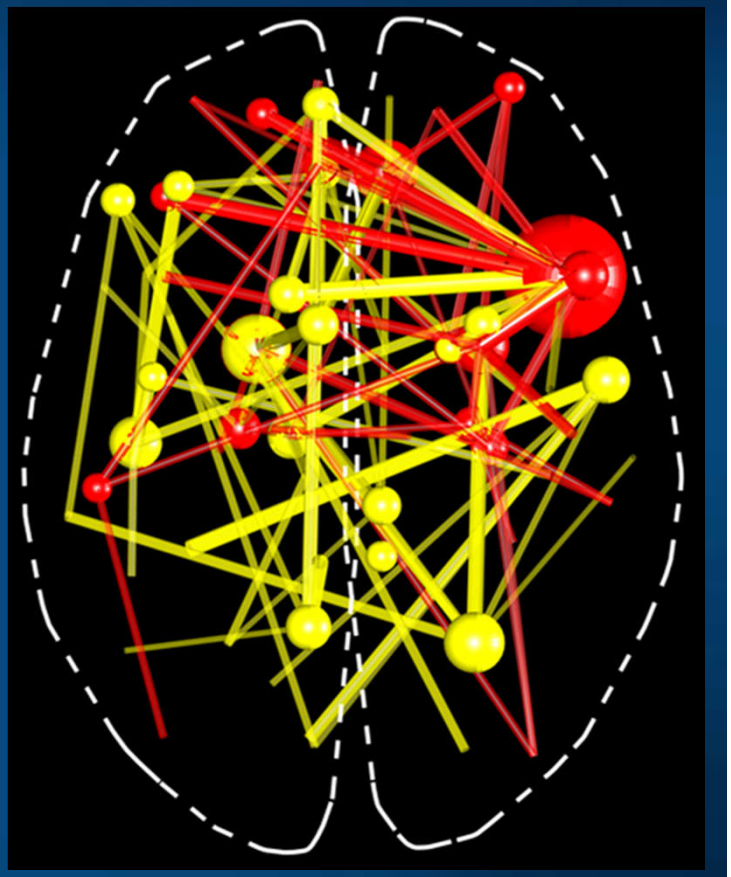
Brain simulations at different levels.

Part III: **Fingerprints of mental activity**.

Neurodynamics on real brain networks.

Past, present, future overview.

2018 OHBM Paris/Singapore brain hackathons overlap with our school …



Part II: Neurodynamics

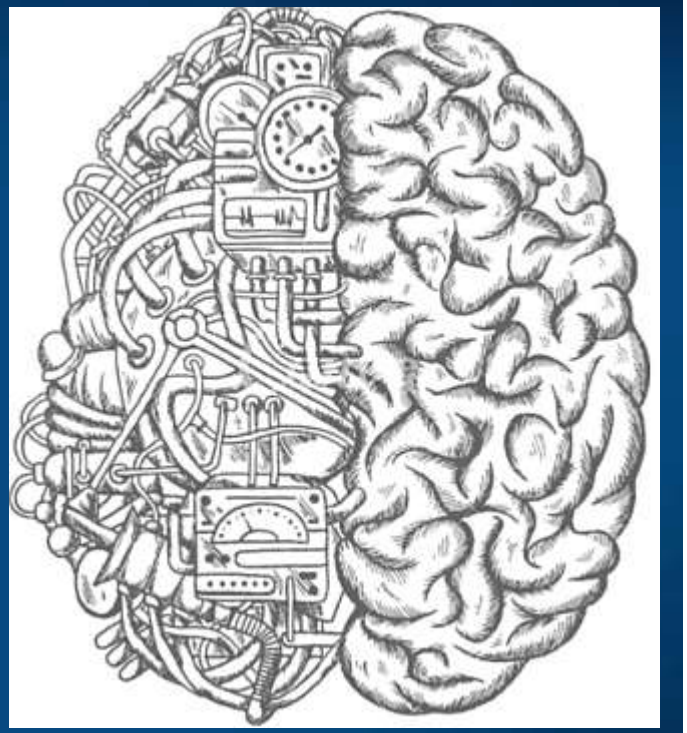
Goal: understanding brains and minds, relations:
Environment ⇔ Brain ⇔ Mind

Cognitive architectures are based on very rough psychological models.

Simple machine learning methods derived from brain inspirations do not explain cognition.

Simulate brain processes => understand brain functions, diseases, derive models based on simple principles.

Neurodynamics is the key, middle level of neuropsychiatric/neurocognitive phenomics.



How to simulate the brain?

HBP has Brain Simulation Platform (BSP, 2016), focused on scaffold models of molecular-level principal neurons and cellular-level reconstructions of cortical and sub-cortical regions, models for implementation in neuromorphic computing systems, and network-level models of the mouse brain.

Computational Neuroscience Software - great list.

Comparison of Neural Network Simulators – O'Reilley's group

Neuron, GENESIS, large and detailed neuron models.

NEST and Brian (Python, spiking neurons).

The Neuroscience Gateway, NSG allows computational neuroscientists to run parallel simulations, free of charge, on supercomputers using tools like GENESIS3, NEURON, MOOSE, NEST, Brian, CARLsim, PyNN, Freesurfer, BluePyOpt, NetPyNE and The Virtual Brain Personalized Multimodal Connectome Pipeline. Python, R and Octave are also available.

The Virtual Brain

Baycrest's Rotman Research Institute (McIntosh, Jirsa, Deco). YouTube

Simulation of large-scale brain networks dynamics, realistic connectivity, tractographic data (DTI/DSI), to generate connectivity matrices and build cortical and subcortical brain networks.

The connectivity matrix defines the connection strengths and time delays via signal transmission between all network nodes. Neural mass models define the mesoscopic dynamics of a network using mean-field model. Many neuropsychiatric applications based on simple population-based models.

TheVirtualBrain simulates and generates the time courses of various forms of neural activity including LFP and firing rate, EEG, MEG and fMRI.
TVB provides all means necessary to generate, manipulate and visualize connectivity and network dynamics; classical time series analysis tools, structural and functional connectivity analysis tools, parameter exploration facilities by launching parallel simulations on a cluster – ex: interpolate fMRI.

A few things you may do with TVB: mmc1.mp4, and mmc1.mp4,
Randy McIntosh presentation.

How brains make up their minds

Gentle intro to Cognitive Neuroscience.

- Brains, Minds, Cognition & Neurocognitive Informatics, and the lab notes.
- Functional Organization of Brains, and the lab notes.
- Neocortex Functions and its Working Styles, and the lab notes.
- Self-organizing, Hebbian and error-driven learning
- Memory, and the lab notes.
- Language, and the lab notes.
- Complex Cognition

Laboratory notes based on the C. O'Reilly and Yuko Munakata, Computational Explorations in Cognitive Neuroscience: Understanding the Mind by Simulating the Brain, Cambridge, MA: MIT Press. New version of this book is here, and the Emergent simulator software is here.
Tutorials based on this software are here.

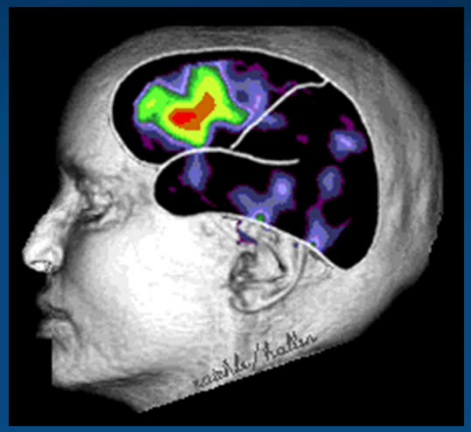
Originally lecture were given at SCE NTU, Singapore (additional by Ahhwee Tan)

Analysis of neurodynamics

Geometric model of mind

Brain ⇔ Psyche

Objective ⇔ Subjective



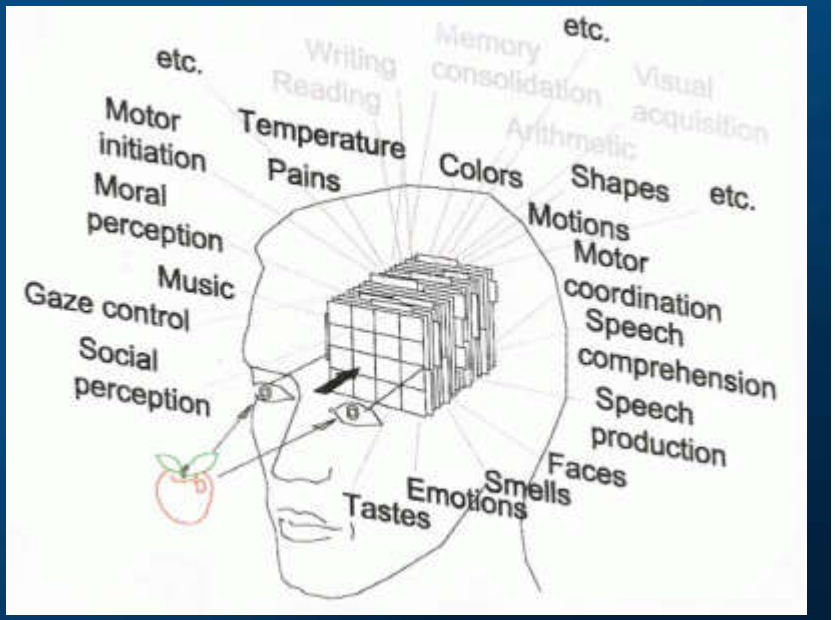
Neurodynamics: bioelectrical activity of the brain, neural activity measured using EEG, MEG, NIRS-OT, PET, fMRI, other techniques.

Mapping S(M)⇔S(B) but how do we describe the state of mind?

Verbal description is not sufficient. A space with dimensions that measure different aspects of experience is needed.

Mental states, movement of thoughts ⇔ trajectories in psychological spaces.

Problem: good phenomenology. We are not able to describe our mental states.

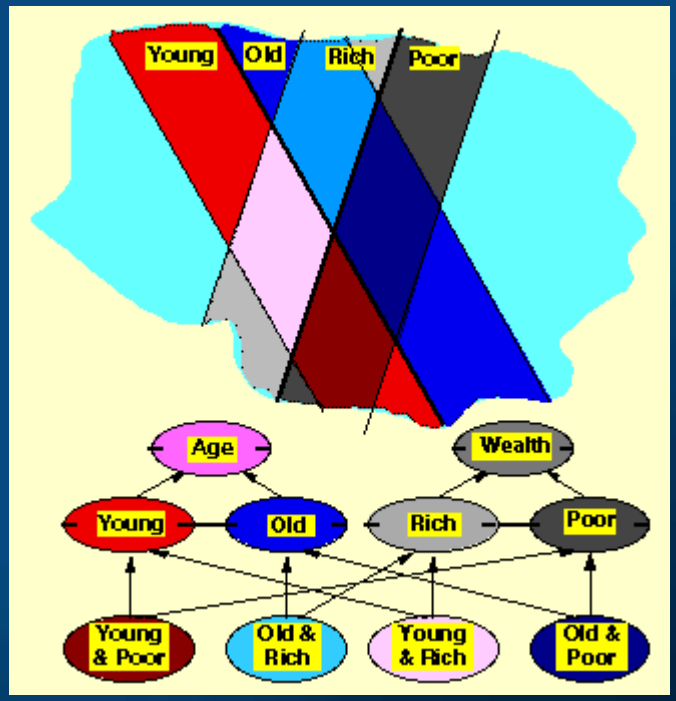


Hurlburt & Schwitzgabel, Describing Inner Experience? MIT Press 2007

P-spaces

Psychological spaces: how to visualize mental states?

K. Lewin, The conceptual representation and the measurement of psychological forces (1938), cognitive dynamic movement in phenomenological space.



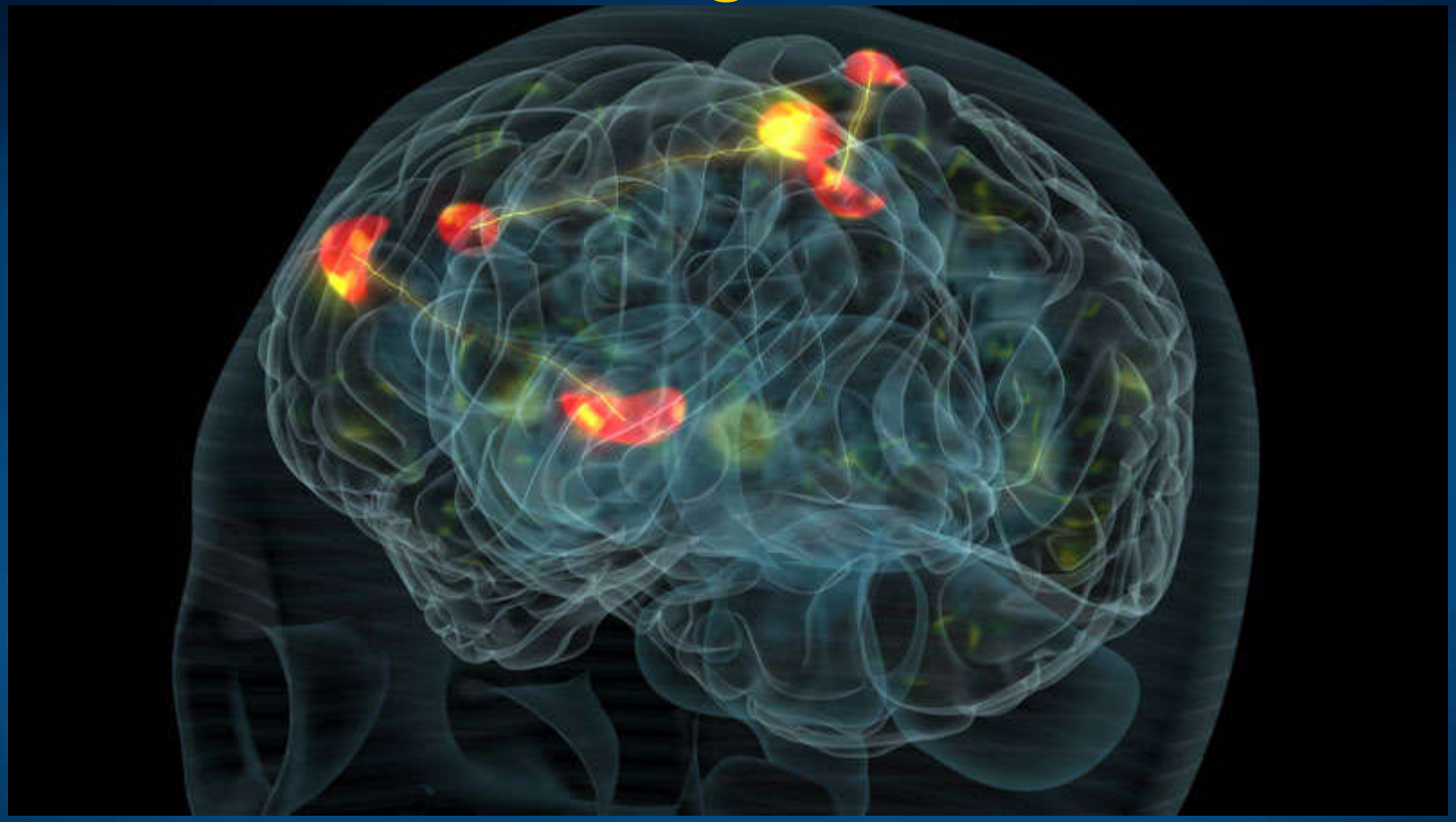
George Kelly (1955):
personal construct psychology (PCP), geometry of psychological spaces as alternative to logic.

A complete theory of cognition, action, learning and intention.

PCP network, society, journal, software … quite active group.

Many things in philosophy, dynamics, neuroscience and psychology, searching for new ways of understanding cognition, are relevant here.

Mental state: strong coherent activation



Many processes go on in parallel, controlling homeostasis and behavior. Most are automatic, hidden from our Self. What goes on in my head?

Various subnetworks compete for access to the highest level of control - consciousness, the winner-takes-most mechanism leaves only the strongest.

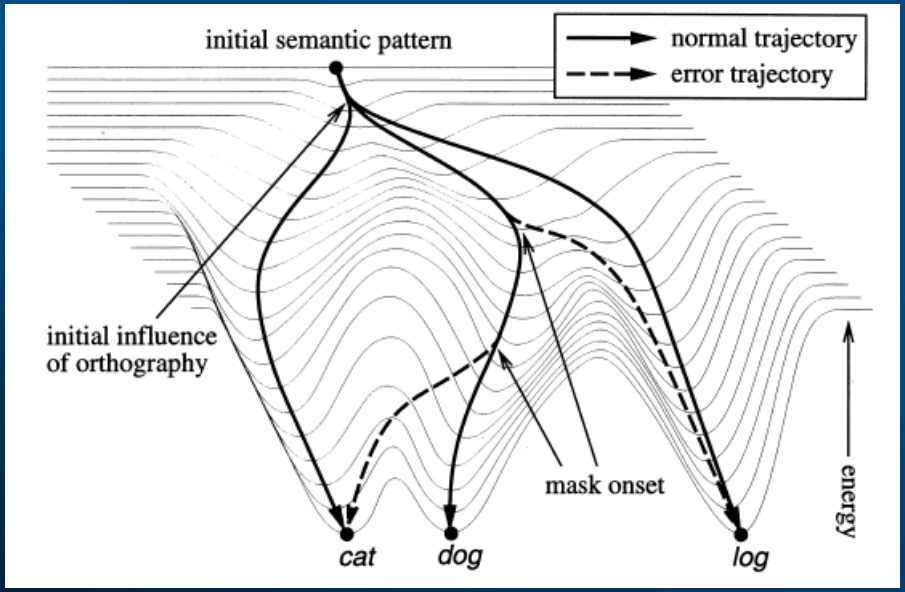
Signal detection theory requires stable microstates!

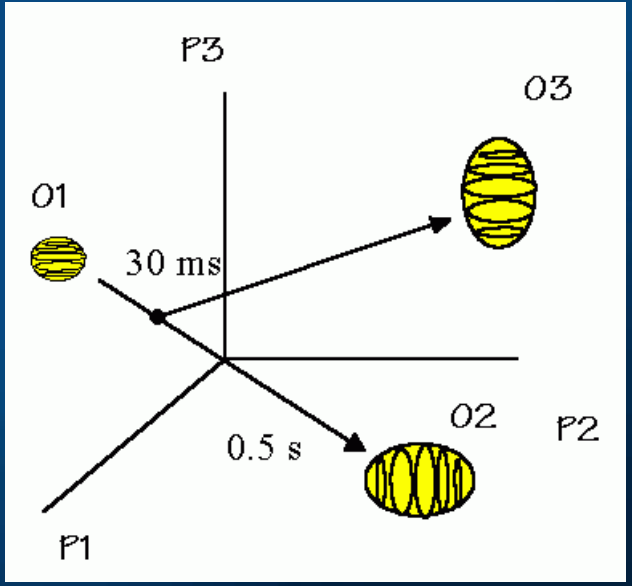
Mental trajectories

P.McLeod, T. Shallice, D.C. Plaut, Attractor dynamics in word recognition: converging evidence from errors by normal subjects, dyslexic patients and a connectionist model. Cognition 74 (2000) 91-113.

M. Spivey, Continuity of mind. 2006.

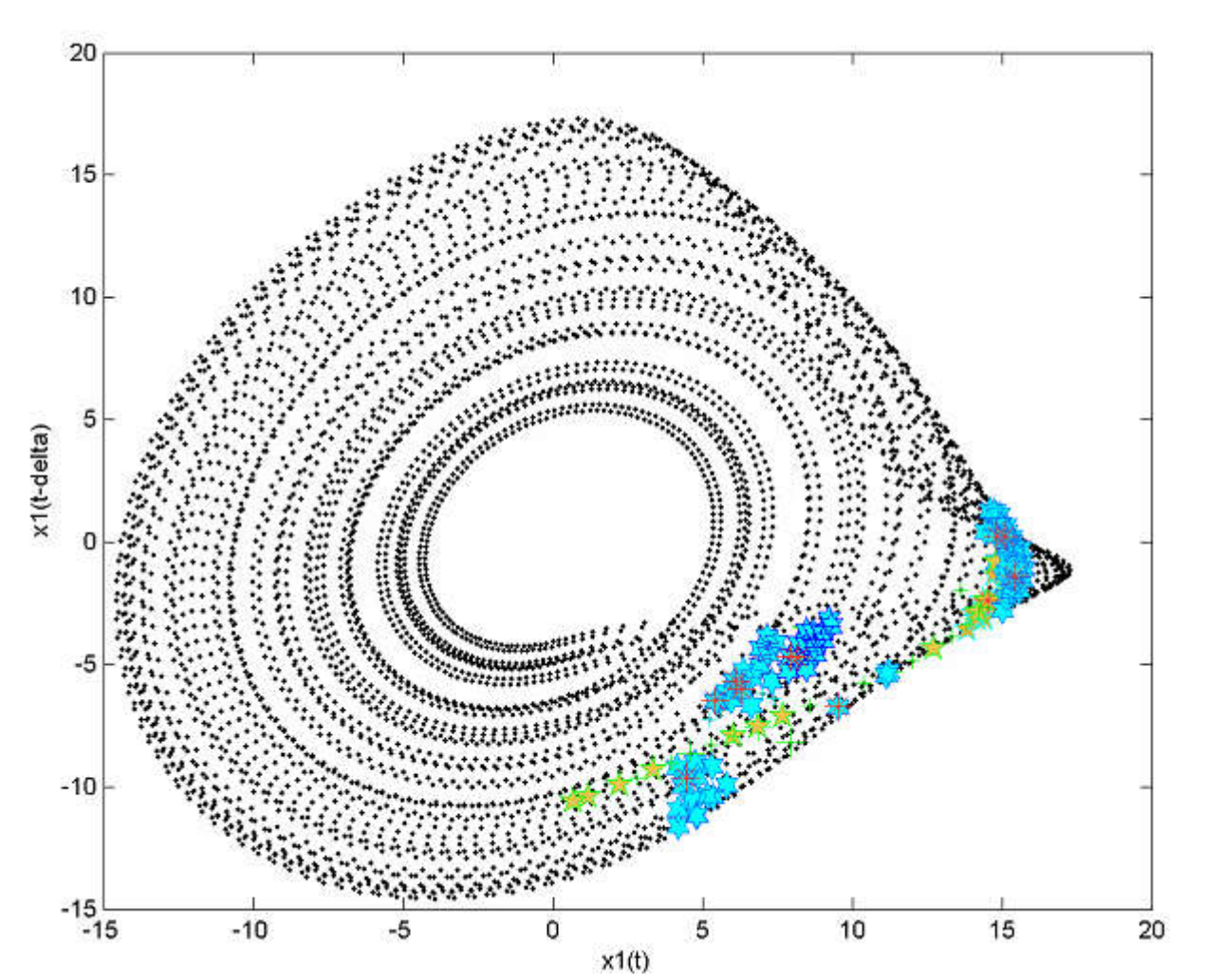
New approach in psycholinguistics: investigation of dynamical cognition, influence of masking on semantic and phonological errors.





Recurrence plots

Embedding of d-dim time series via Taken's theorem: $x(t)$ is replaced by a vector $Y(t)=(x(t);x(t-\delta);\ \ldots\ x(t-k\delta))$. This recreates original dynamics for $k=2d+1$.



Unfold the trajectory at t and show when it comes close to $x(t)$.

Recurrence plots

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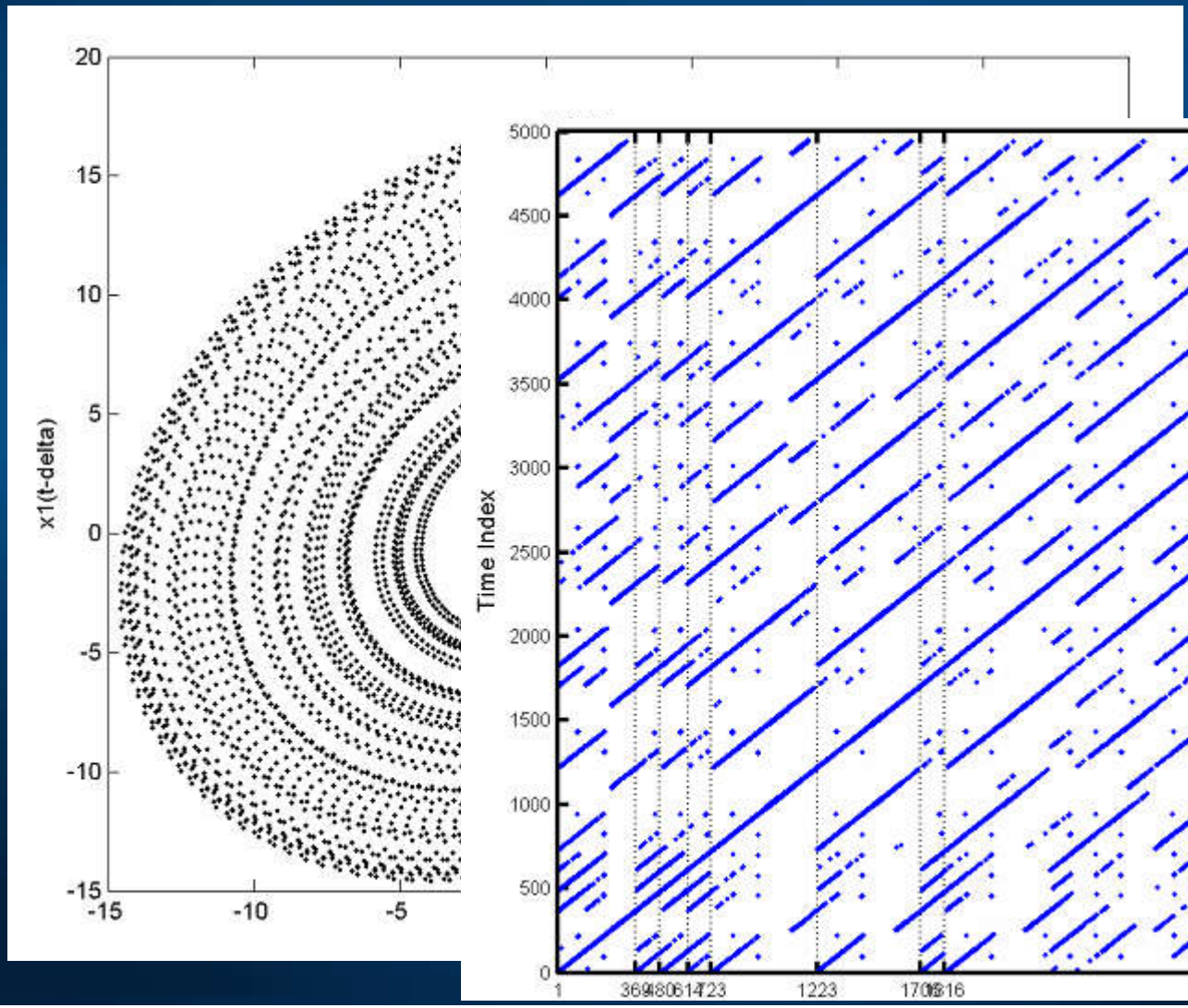


Unfold the trajectory

Recurrence plots

Trajectory of dynamical system (neural activities) may be visualized using recurrence plots (RP).

$$\mathbf{x}(t) = \{x_i(t)\}_{i=1..n}^{t=1..N}$$

Poincaré (1890) proved recurrence theorem:

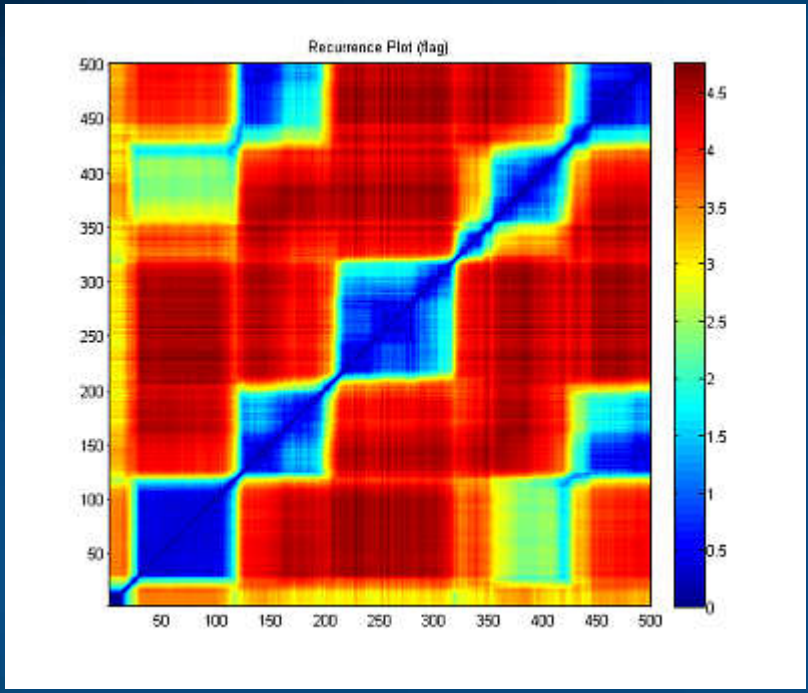
If we have a measure preserving transformation, the trajectory will eventually come back to the neighbourhood of any former point with probability one.

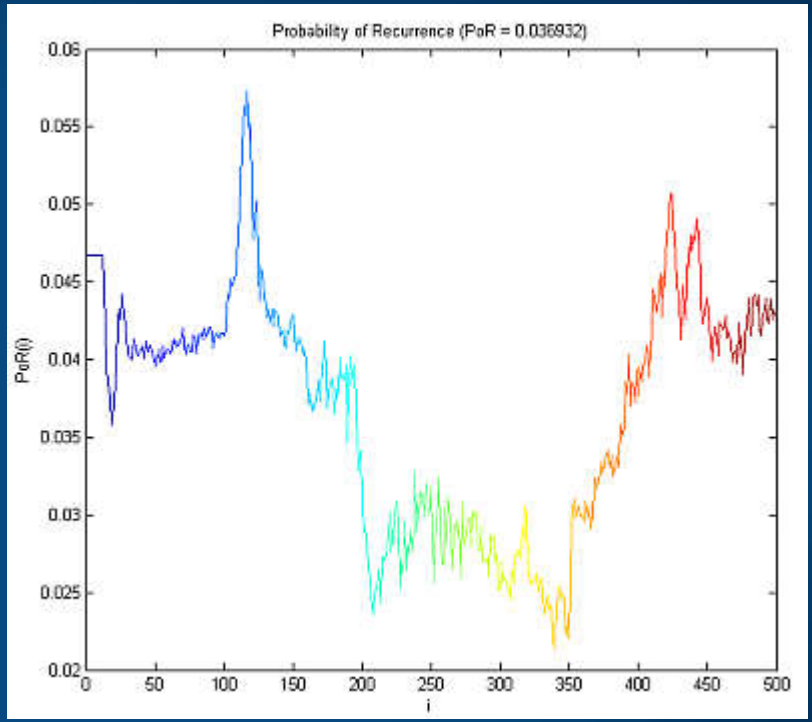
$$R(t,t';\varepsilon) = \Theta\left(\varepsilon - \left\|x(t) - x(t')\right\|\right) \quad R_{ij} = \begin{cases} 1 : x_i \approx x_j \\ 0 : x_i \not\approx x_j \end{cases}$$

R is recurrence matrix based on approximate equality of N trajectory points. For discretized time steps binary matrix $\boldsymbol{R}_{ij}$ is obtained.

Many measures of complexity and dynamical invariants are derived from RP matrices: generalized entropies, correlation dimensions, mutual information, redundancies, etc. Great intro: N. Marwan et al, Recurrence plots for the analysis of complex system. Physics Reports 438 (2007) 237–329

Probability of recurrence





Probability of recurrence may be computed from recurrence plots, or from clusterization of trajectory points, allowing for evaluation how strongly some basins of attractors capture neurodynamics.

Our Viser Toolbox is used for such visualizations (K. Dobosz, WD)

Non-linear features from RPs

Features: Nonlinear invariant measures of a time series and their physical interpretation, recurrence quantification analysis (RQA).

1. Sample Entropy (SampE)
2. Detrended Fluctuation Analysis (DFA), statistical self-affinity of a signal.
3. Entropy derived from recurrence plot (L_entr)
4. Max. line length (L_max), largest Lyapunov exponent
5. Mean line length (L_mean), mean prediction time of the signal
6. Recurrence rate (RR), probability of recurrence
7. Determinism (DET), repeating patterns in the system
8. Laminarity (LAM), frequency of transitions between states
9. Trapping time (TT), time in a given state

Bosl, WJ, Tager-Flusberg, H, & Nelson, CA (2018). EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach. *Scientific Reports*, *8*(1), 6828.

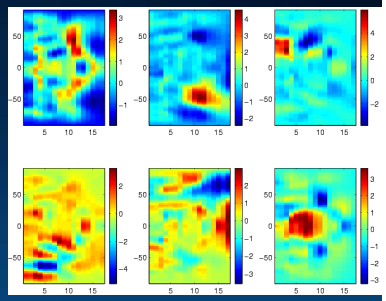
19/out of 128 electrodes selected, 3-36 month old, ~ 95% success …

Symbolic Dynamics (SD)

SD: dynamical system is modeled by a discrete space of sequences of abstract symbols (states of the system). Dynamics is given by the shift operator, generating a discrete-time Markov process. In practice:

- Phase space is partitioned into regions labeled with different symbols A_i
- Every time the system trajectory is found in one of these regions appropriate symbol is emitted.
- Sequence of symbols gives a coarse-grained description of dynamics that can be analyzed using statistical tools, ex: A_1, A_2, A_1, A_4, A_3 ….
- Although discretization of continuous dynamical states looses the fluid nature of cognition, symbolic dynamics gives an appropriate framework for cognitive representations (Spivey, Continuity of mind, 2007)
- SD is used for low-d systems. In high-d partitioning phase spaces will contain a huge number of regions with sharply defined boundaries, and sequences are not easy to comprehend.
- We are mostly interested in high-d dynamical systems, d>100.

FSD is good for you!



- Fuzzy symbolic dynamics is a natural way to generalize the notion of symbolic dynamics and recurrence plots.
- FSD provides dimensionality reduction, non-linear mapping for visualization of trajectories, shows various aspects of dynamics that are difficult to discover looking at individual components, local trajectory clusters and their relations.
- FSD can be applied to raw signals, transformed signals (ex. ICA/PCA components), or to signals in the time-frequency domain.
- Key: good reference points for membership functions.

Dobosz K, Duch W. (2010) Understanding Neurodynamical Systems via Fuzzy Symbolic Dynamics. Neural Networks Vol. 23 (2010) 487-496

Duch W, Dobosz K, *Visualization for Understanding of Neurodynamical Systems.* Cognitive Neurodynamics 5(2), 145-160, 2011.

Fuzzy Symbolic Dynamics (FSD)

$$R(t,t';\varepsilon) = \Theta\left(\varepsilon - \left\| x(t) - x(t') \right\|\right)$$

R matrix with real distances, or distances from reference points:

$$S(\mathbf{x}(t), \mathbf{x}_0) = \Theta\left(\varepsilon - \left\| \mathbf{x}(t) - \mathbf{x}_0 \right\|\right) => \exp\left(-\left\| \mathbf{x}(t) - \mathbf{x}_0 \right\|\right)$$

1. Standardize original data in high dimensional space.
2. Find cluster centers (e.g. by k-means algorithm): $\mu_1, \mu_2 \ldots \mu_d$
3. Use non-linear mapping to reduce dimensionality to d, for example:

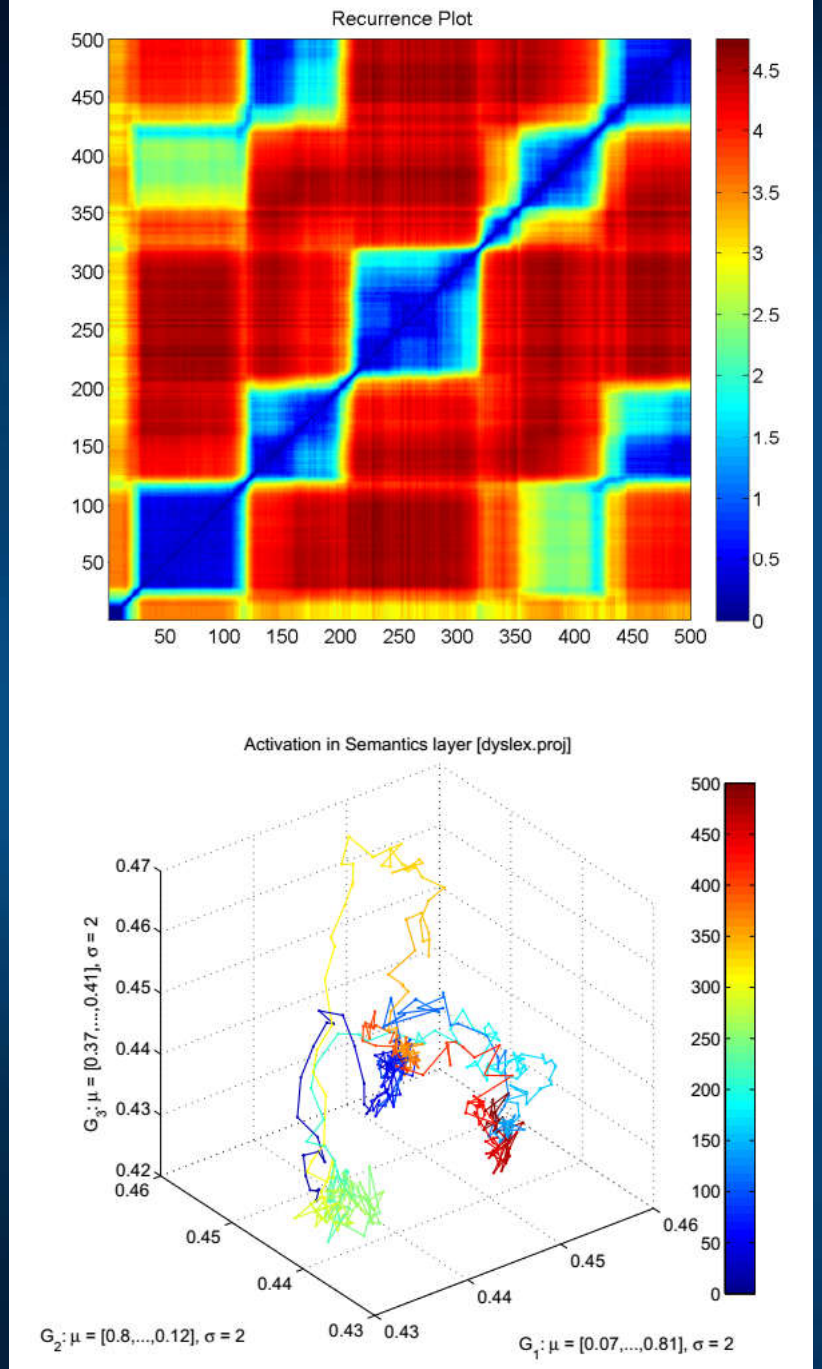
$$y_k(t;\mu_k,\Sigma_k) = \exp\left(-\left(x-\mu_k\right)^{\mathrm{T}} \Sigma_k^{-1} \left(x-\mu_k\right)\right)$$

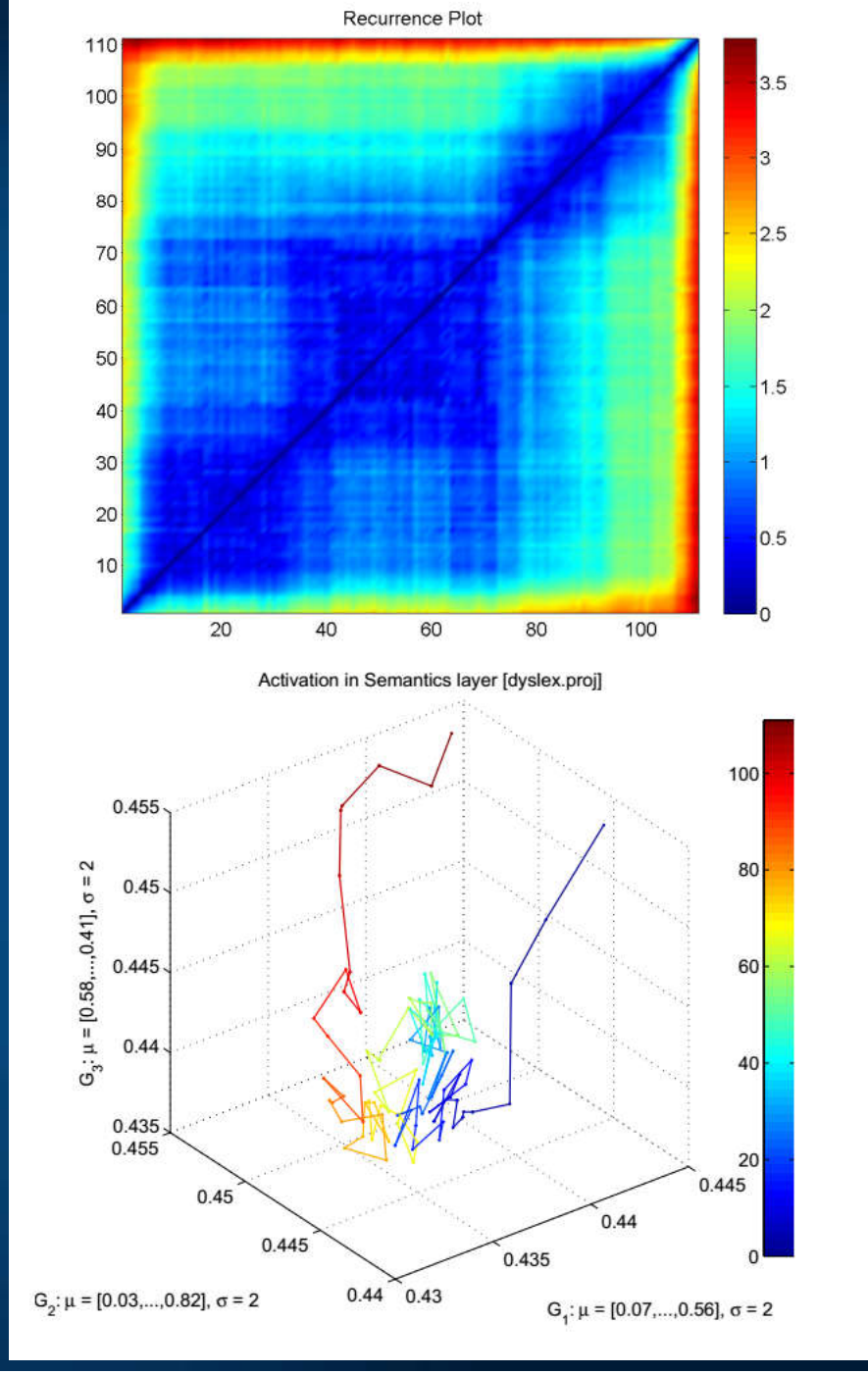
Localized membership functions $y_k(t;W)$:

sharp indicator functions => symbolic dynamics; $x(t)$ => strings of symbols;

soft functions => fuzzy symbolic dynamics, dimensionality reduction

$Y(t)=(y_1(t;W), y_2(t;W))$ => visualization of high-dim data.


Recurrence Plot
Activation in Semantics layer [dyslex.proj]
G2: μ = [0.8,...,0.12], σ = 2
G1: μ = [0.07,...,0.81], σ = 2
G3: μ = [0.37,...,0.41], σ = 2


Recurrence Plot
Activation in Semantics layer [dyslex.proj]
G2: μ = [0.03,...,0.82], σ = 2
G1: μ = [0.07,...,0.56], σ = 2
G3: μ = [0.58,...,0.41], σ = 2

FSD development

- Optimization of parameters of membership functions to see more structure from the point of view of relevant task.
- Selection of relevant dimensions to see hidden structure.
- Learning: supervised clustering, projection pursuit based on quality of clusters => projection on interesting directions.
- Visualization in 3D and higher (lattice projections, etc).
- Quantification of Recurrence Plots (Recurrence Quantification Analysis)
- Other measures to characterize dynamics: position and size of basins of attractors, transition probabilities, types of oscillations around each attractor (follow theory of recurrent plots for more).
- Calibrating our eyes: more tests on model data and on the real data.

Optimization of FSD parameters

- Find centers of attractors (clusters) $\mathbf{P}_i$ and calculated distances:

$$\mathbf{D}_{ij} = \|\mathbf{P}_i - \mathbf{P}_j\| \,.$$

- Map $\mathbf{P}_i$ to low (2 or 3) $\bar{d}$ space using Gaussian functions:

$$\mathbf{G}(\mathbf{P}_i; \mathbf{Q}_k, \sigma_k) = [G_k(\mathbf{P}_i; \mathbf{Q}_k, \sigma_k)]_{k=1,\ldots,\bar{d}} \,,$$

- To preserve distances D_{ij} in low-d space calculate g_{ij}

$$g_{ij}(\mathbf{Q}_k, \sigma_k) = \|\mathbf{G}(\mathbf{P}_i; \mathbf{Q}_k, \sigma_k) - \mathbf{G}(\mathbf{P}_j; \mathbf{Q}_k, \sigma_k)\| \,.$$

- and minimize stress function:

$$\mathcal{I}(\mathbf{Q}_k, \sigma_k) = \sum_{i>j} \|g_{ij}(\mathbf{Q}_k, \sigma_k) - \mathbf{D}_{ij}\| \,,$$

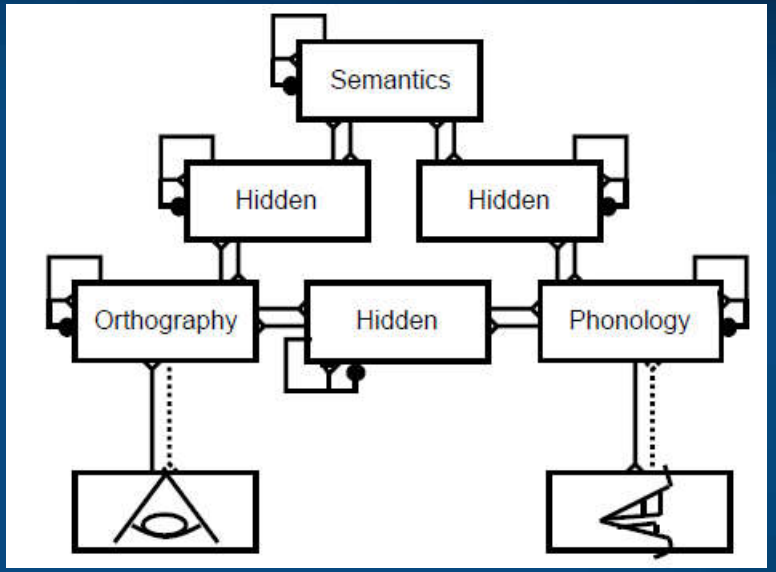
to find best positions $\mathbf{Q}_k$ (+ and dispersions σ_k), $k = 1, \ldots, \bar{d}$

- Simpler minimization: select only a few smallest distances.

Brain networks: neurolinguistics.

Reading and dyslexia

Phonological dyslexia: deficit in reading pronounceable nonwords (e.g., “nust” (Wernicke).

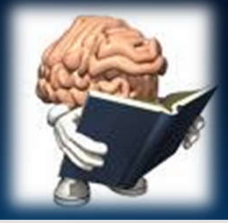


Deep dyslexia like phonological dyslexia + significant levels of semantic errors, reading for ex. “dog” as “cat”.

Surface dyslexia: preserved ability to read nonwords, impairments in retrieving semantic information from written words, difficulty in reading exception, low-frequency words, ex. “yacht.”
Surface dyslexia - visual errors, but not semantic errors. .

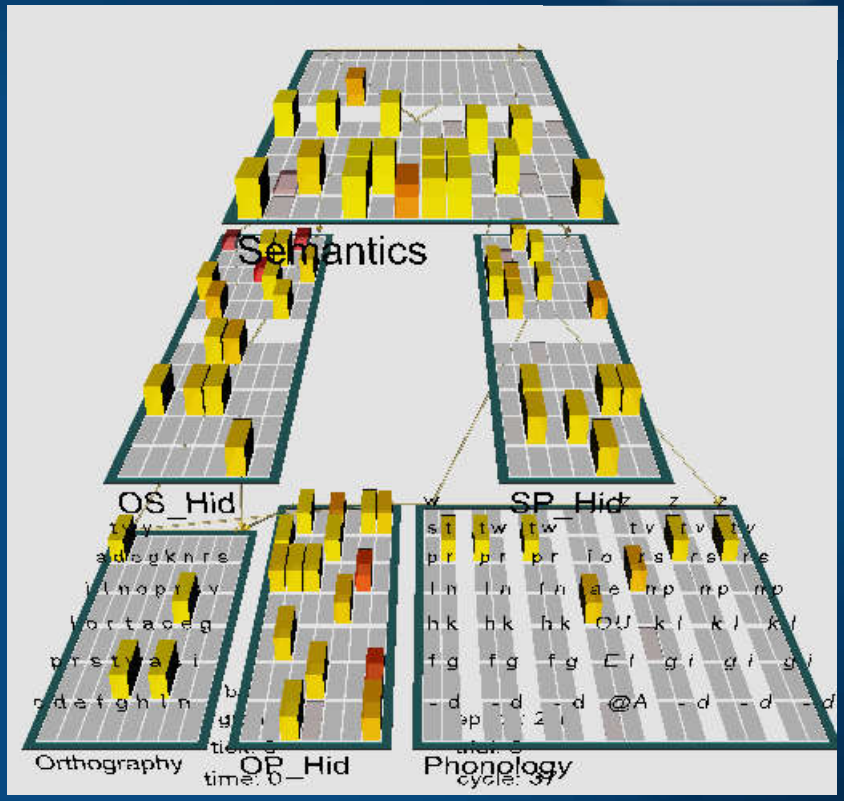
Double route model of dyslexia includes orthography, phonology, and semantic layers, direct ortho=Phono route and indirect ortho => semantics => phono, allowing to pronounce rare words.

Model of reading



Emergent neural simulator:

Aisa, B., Mingus, B., and O'Reilly, R. The emergent neural modeling system. Neural Networks, 21, 1045-1212, 2008.



3-layer model of reading:

orthography, phonology, semantics, or distribution of activity over 140 microfeatures of concepts.

Hidden layers in between.

Neurons ~20 parameters, excitation, inhibition, leak currents.

Learning: mapping one of the 3 layers to the other two.

Fluctuations around final configuration = attractors representing concepts.

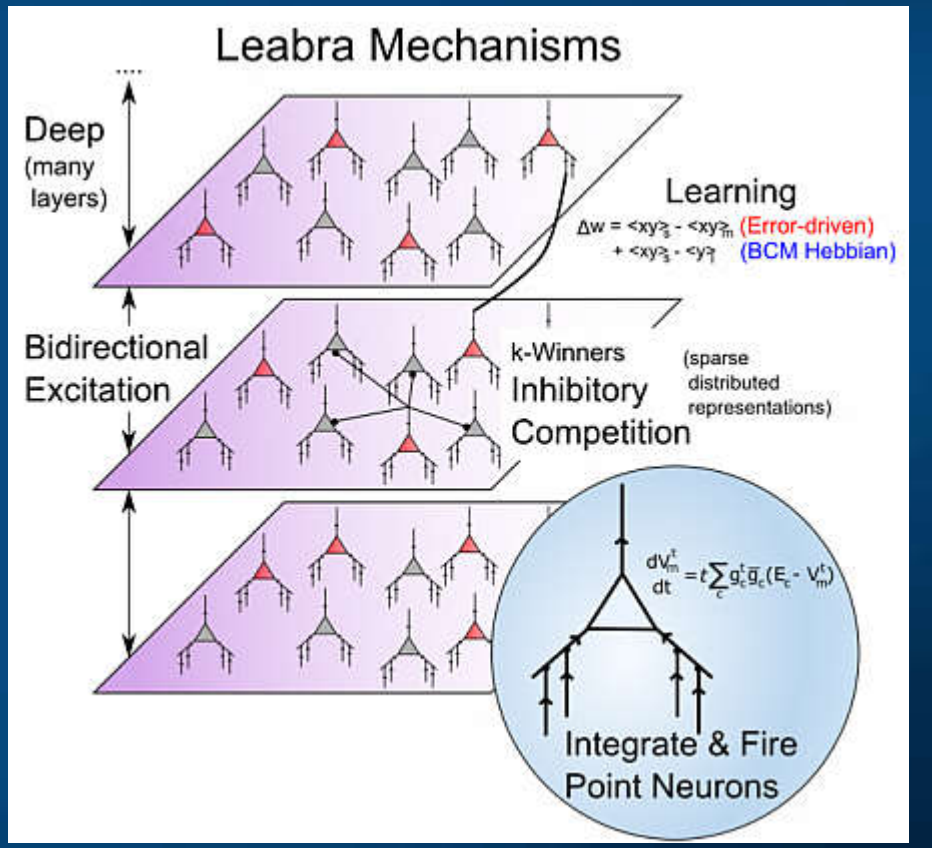
How to see properties of their basins, their relations?

Leabra learning model

Emergent is using Leabra model = *Learning in an Error-driven and Associative, Biologically Realistic Algorithm*

So far we are discussing only how local learning is possible, but all this has to be embedded in overall cognitive architecture.

6 principles embedded in Leabra:
1. integrate & fire point neurons,
2. kWTA, k-winners take all,
3. sparse distributed reps,
4. many layers of transformation,
5. Hebb correlation learning
6. error correction learning.



Computational Models

Models at various level of detail.

- Minimal model includes neurons with 3 types of ion channels.

Models of attention:

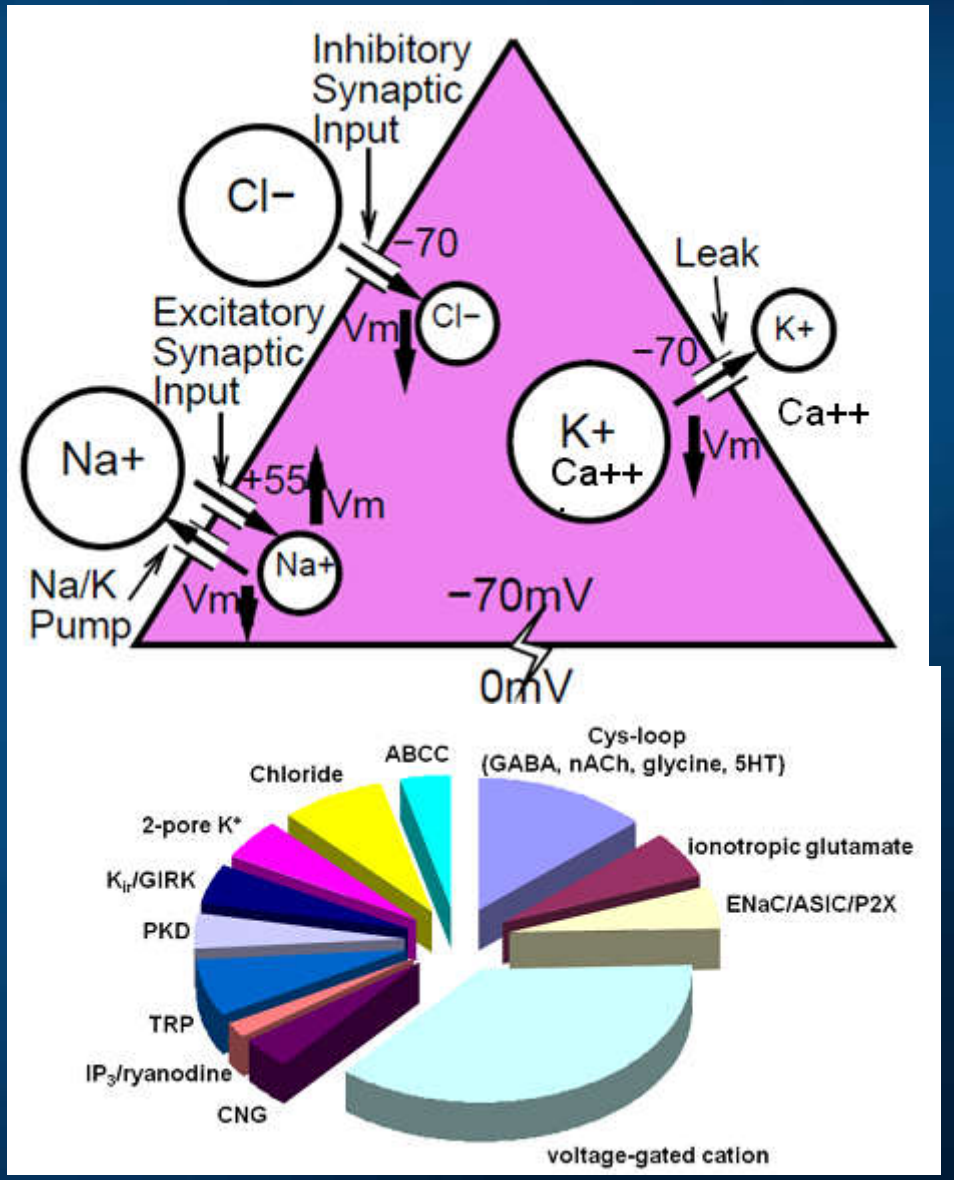
- Posner spatial attention;
- attention shift between visual objects.

Models of word associations:

- sequence of spontaneous thoughts.

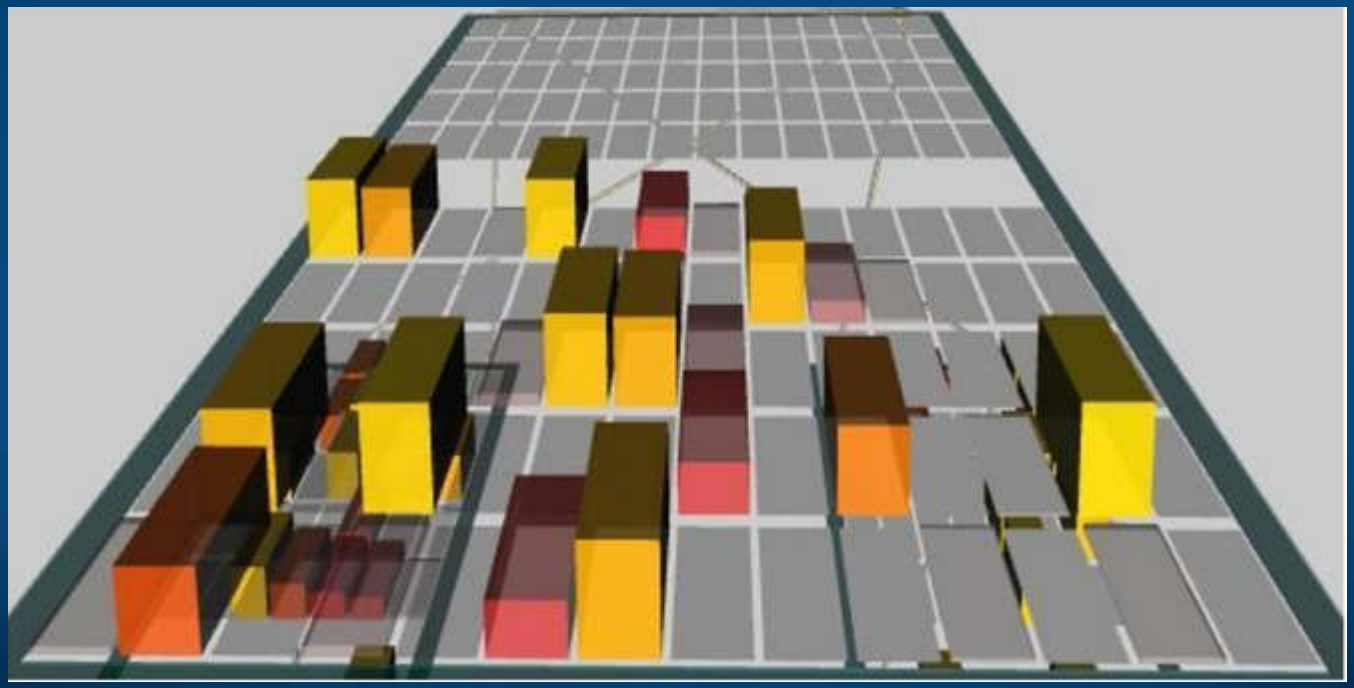
Models of motor control.

Critical: control of the increase in intracellular calcium, which builds up slowly as a function of activation.
Initial focus on the leak channels, 2-pore K^+, looking for genes/proteins.



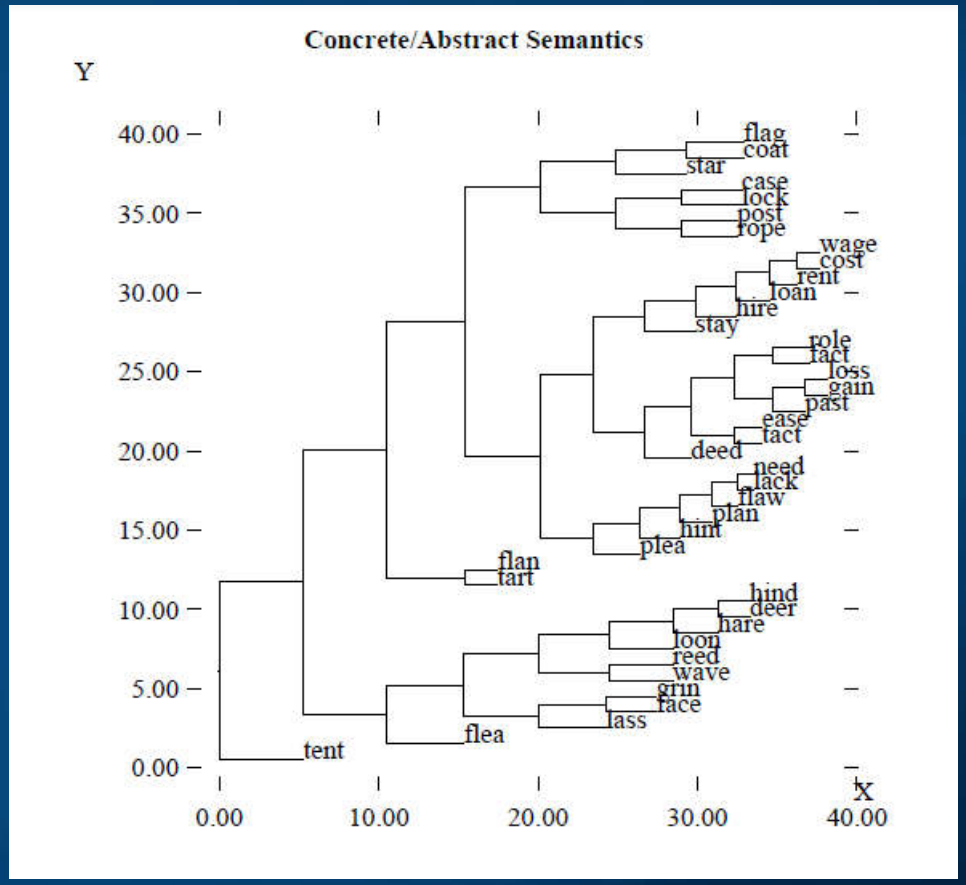
Semantic layer

Semantic layer has 140 units; here activity for the “case” word is shown, upper 70 units code abstract microfeatures, lower physical.



Words to read

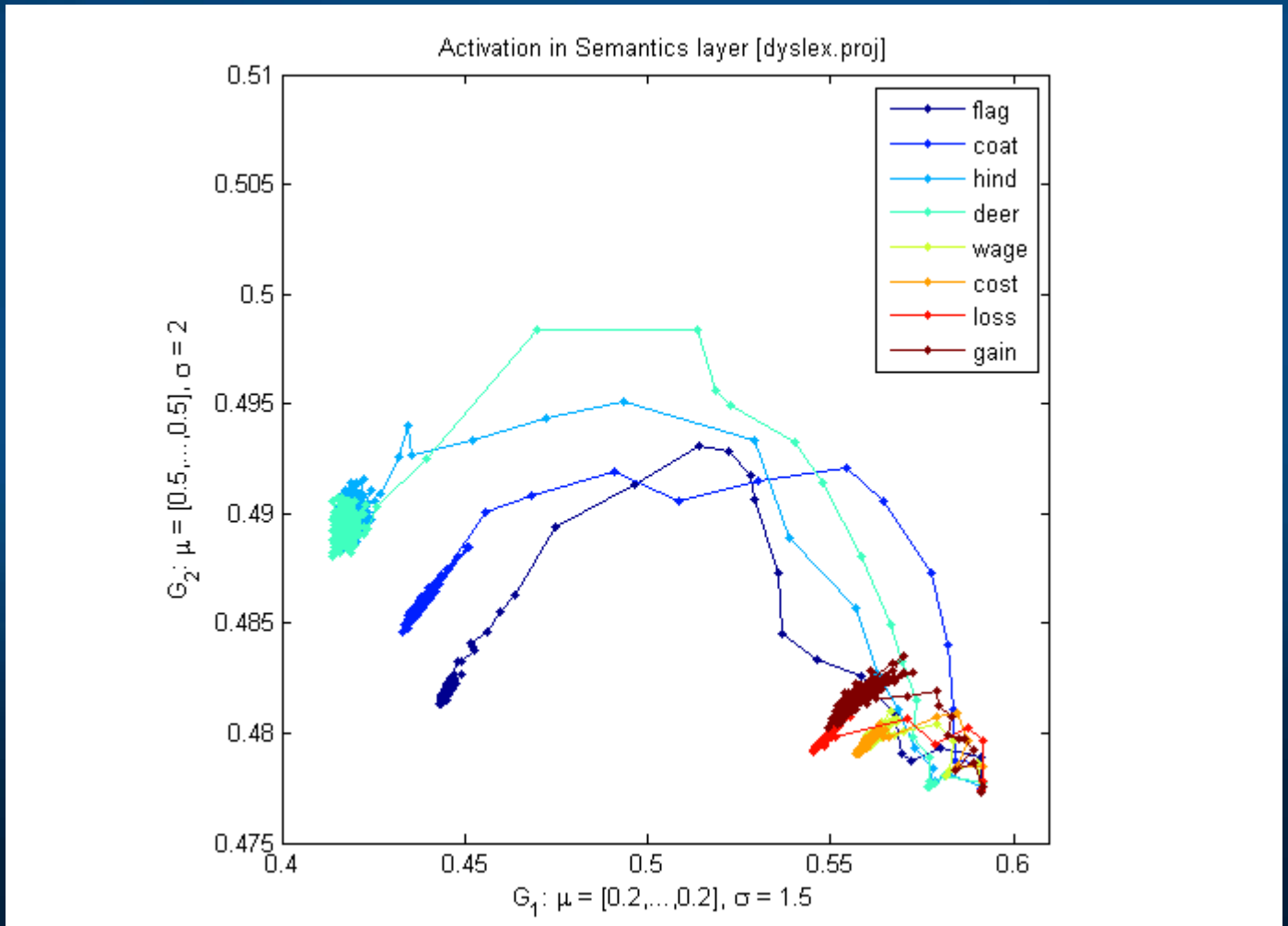
Conc	Phon	Abst	Phon
tart	tttartt	tact	ttt@ktt
tent	tttentt	rent	rrrentt
face	fffAsss	fact	fff@ktt
deer	dddErrr	deed	dddEddd
coat	kkkOttt	cost	kkkostt
grin	grrinnn	gain	gggAnnn
lock	lllakkk	lack	lll@kkk
rope	rrrOppp	role	rrrOlll
hare	hhhArrr	hire	hhhIrrr
lass	lll@sss	loss	lllosss
flan	fllonnn	plan	pll@nnn
hind	hhhIndd	hint	hhhintt
wave	wwwAvvv	wage	wwwAjjj
flea	fllE---	plea	pllE---
star	sttarrr	stay	sttA---
reed	rrrEddd	need	nnnEddd
loon	lllUnnn	loan	lllOnnn
case	kkkAsss	ease	---Ezzz
flag	fll@ggg	flaw	fllo---
post	pppOstt	past	ppp@stt



40 words, 20 abstract & 20 concrete; dendrogram shows similarity in phonological and semantic layers after training.

2D attractors for words

Dobosz K, Duch W, Fuzzy Symbolic Dynamics for Neurodynamical Systems. Neural Networks (in print, 2009). Same 8 words, more synaptic noise.



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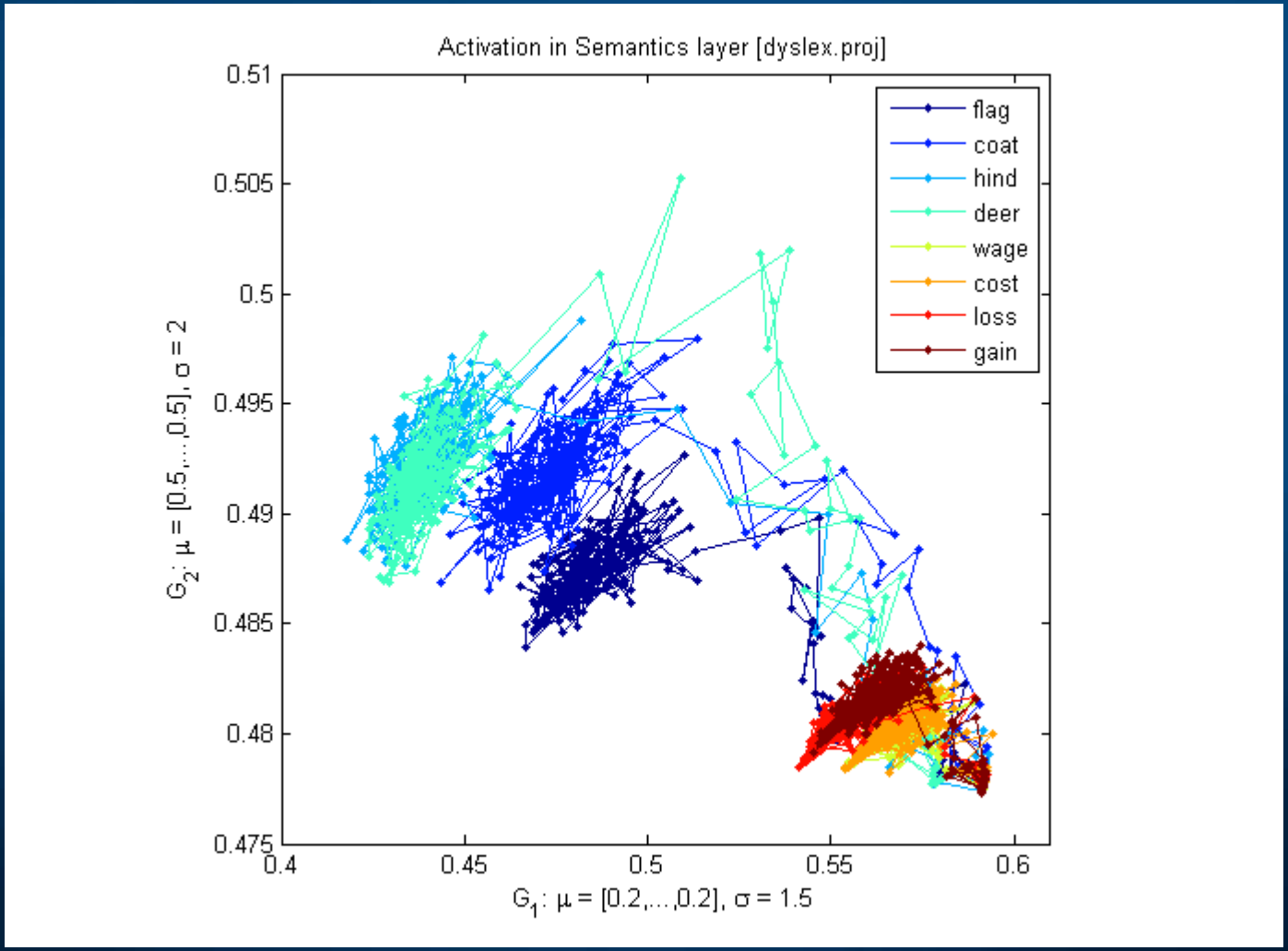
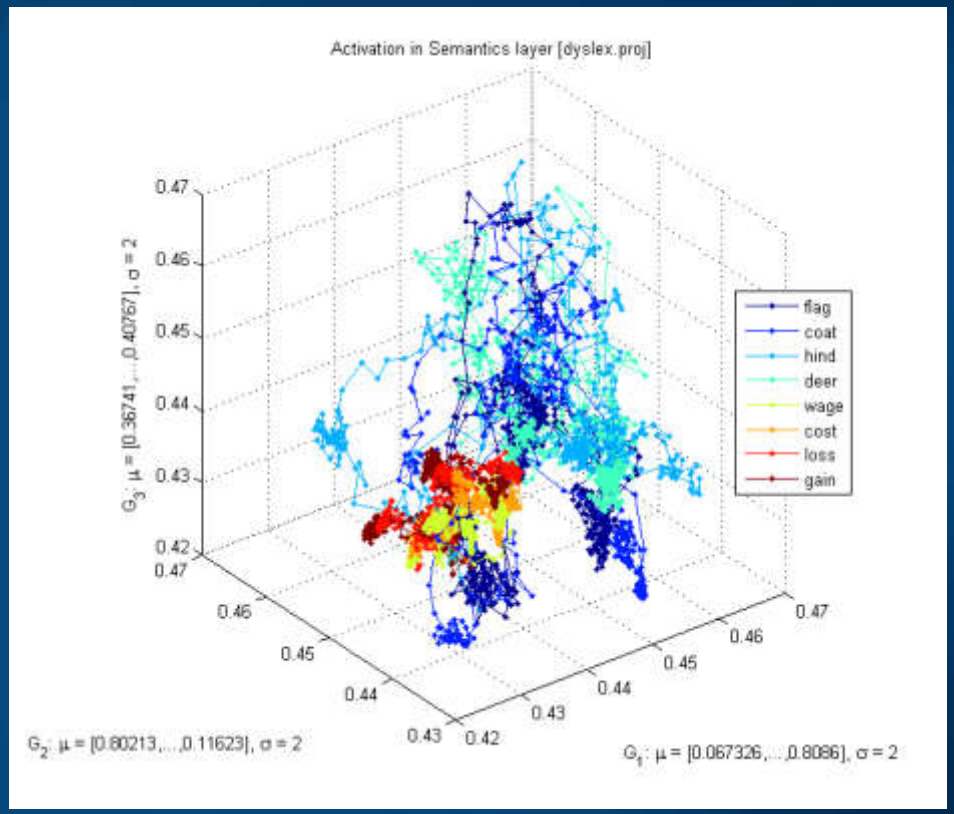


3D attractors for words

Non-linear visualization of activity of the semantic layer with 140 units for the model of reading that includes phonological, orthographic and semantic layers + hidden layers.

Cost /wage, hind/deer have semantic associations, attractors are close to each other, but without neuron accommodation attractor basins are tight and narrow, poor generalization expected.



Training with more variance in phonological and written form of words may help to increase attractor basins and improve generalization.

Attractors

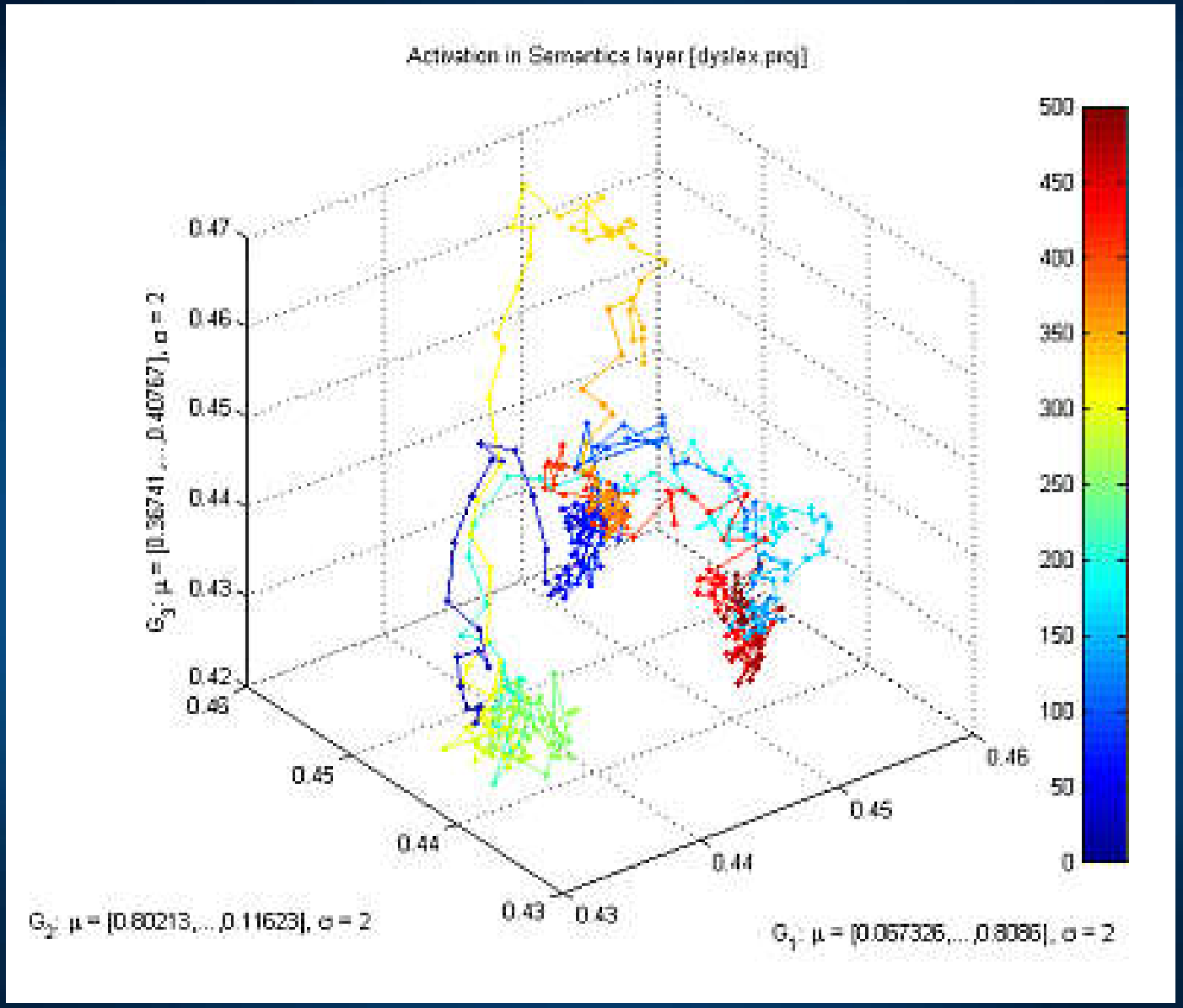
Basins of attractors: input activations {LGN(X)}=> object recognition

Attention – focus on results from:

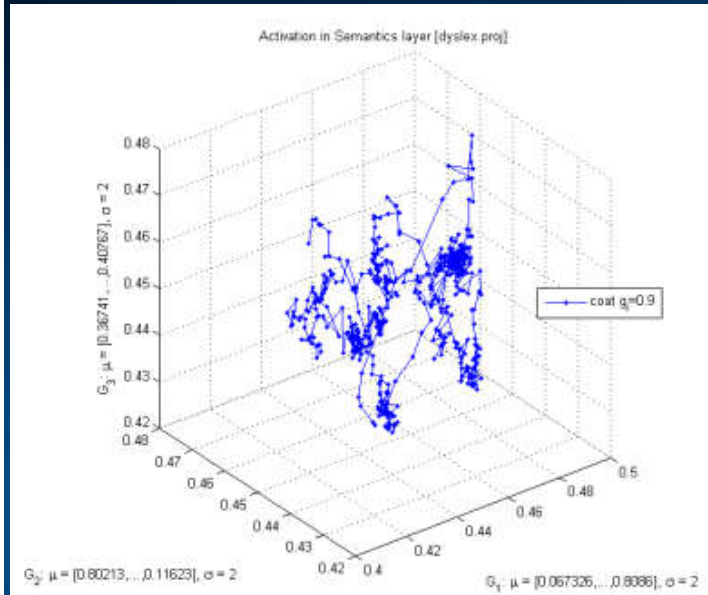
- inhibitory competition,
- bidirectional interactive processing,
- multiple constraint satisfaction.

- Normal case: relatively large, easy associations, moving from one basin of attraction to another, exploring the activation space.
- Without accommodation (voltage-dependent K^+ channels): deep, narrow basins, hard to move out of the basin, associations are weak.

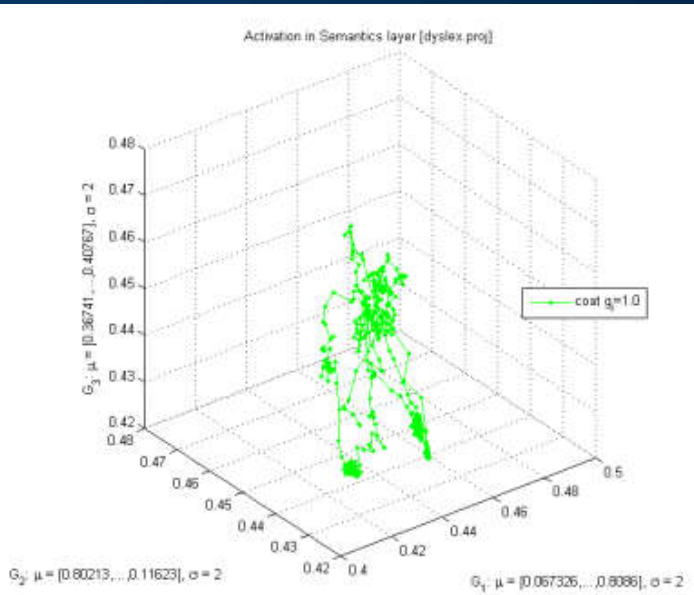
Accommodation: basins of attractors shrink and vanish because neurons desynchronize due to the fatigue; this allows other neurons to synchronize, leading to quite unrelated concepts (thoughts).


Activation in Semantics layer [dyslex.proj]
0.47
0.46
0.45
0.44
0.43
0.42
0.46
0.45
0.44
0.43
0.43
0.44
0.45
0.46
500
450
400
350
300
250
200
150
100
50
0

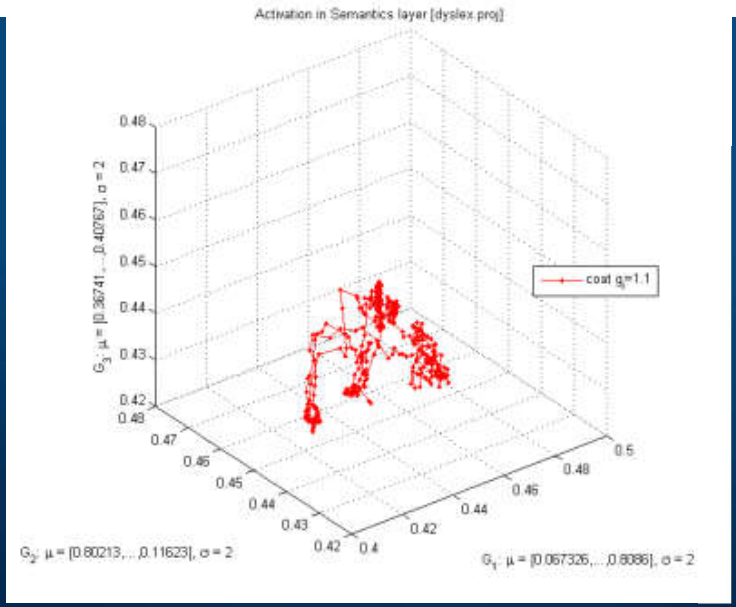
Inhibition



Prompting the system with single word and following noisy dynamics. Not all attractors are real words, some are spurious.

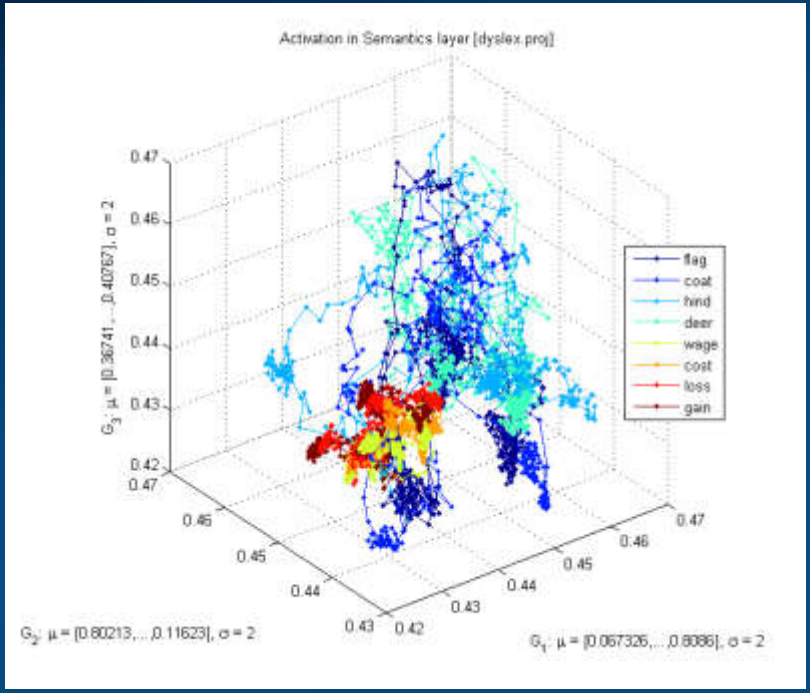


Increasing g_i from 0.9 to 1.1 reduces the attractor basin sizes and simplifies trajectories.

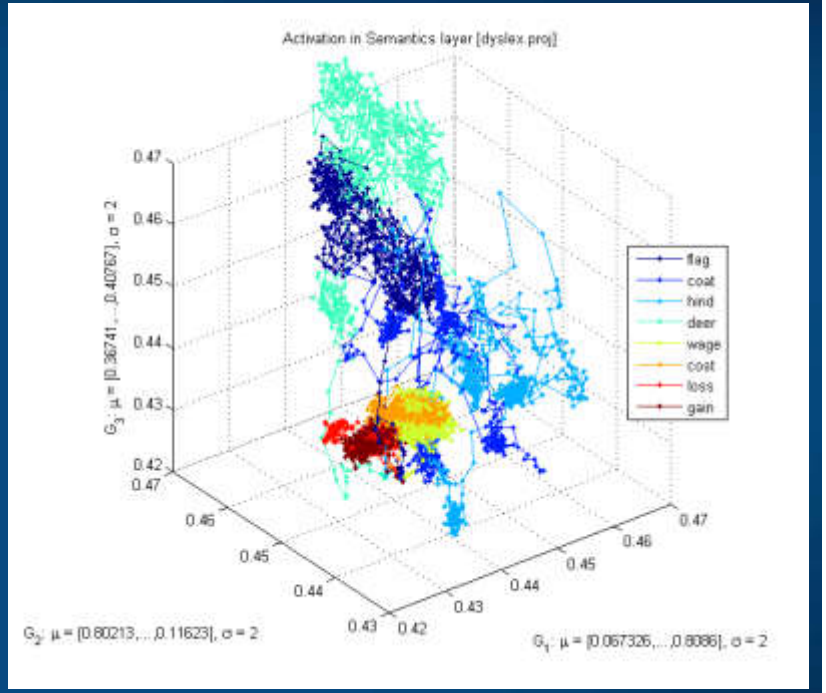


Strong inhibition, empty head …

Connectivity effects

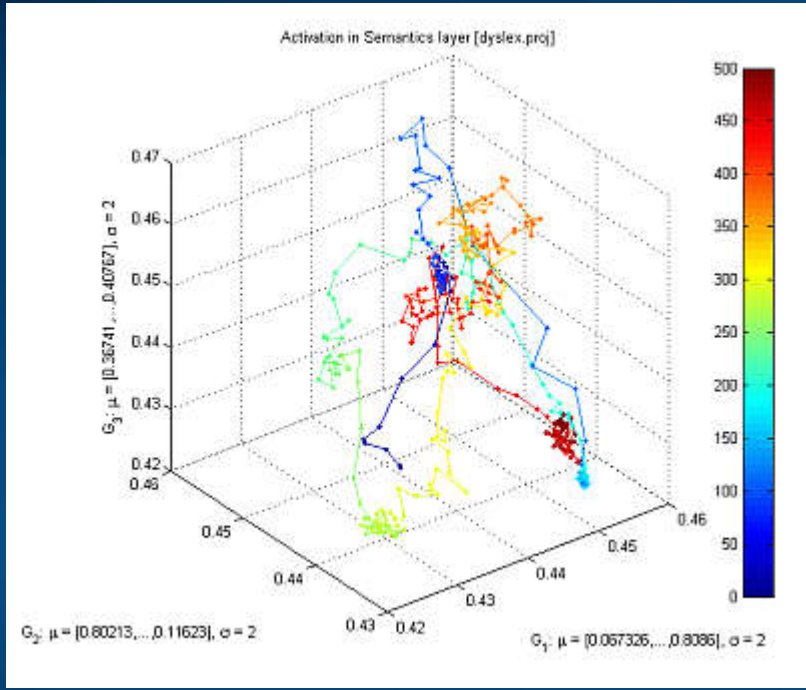


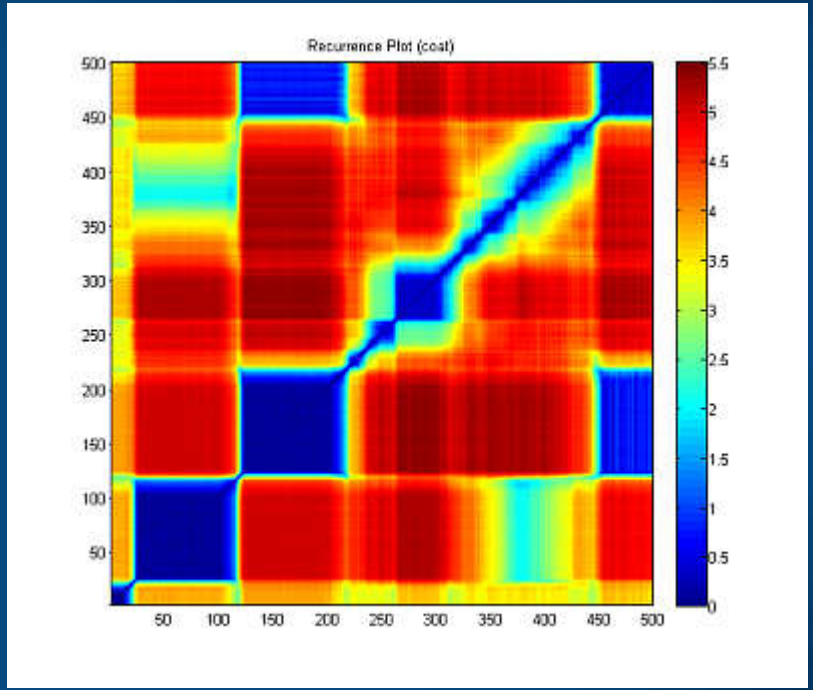
With small synaptic noise (var=0.02) the network starts from reaching an attractor and moves to another one (frequently quite distant), creating a “chain of thoughts”.



Same situation but recurrent connections within layers are stronger, fewer but larger attractors are reached, more time is spent in each attractor.

Fast transitions



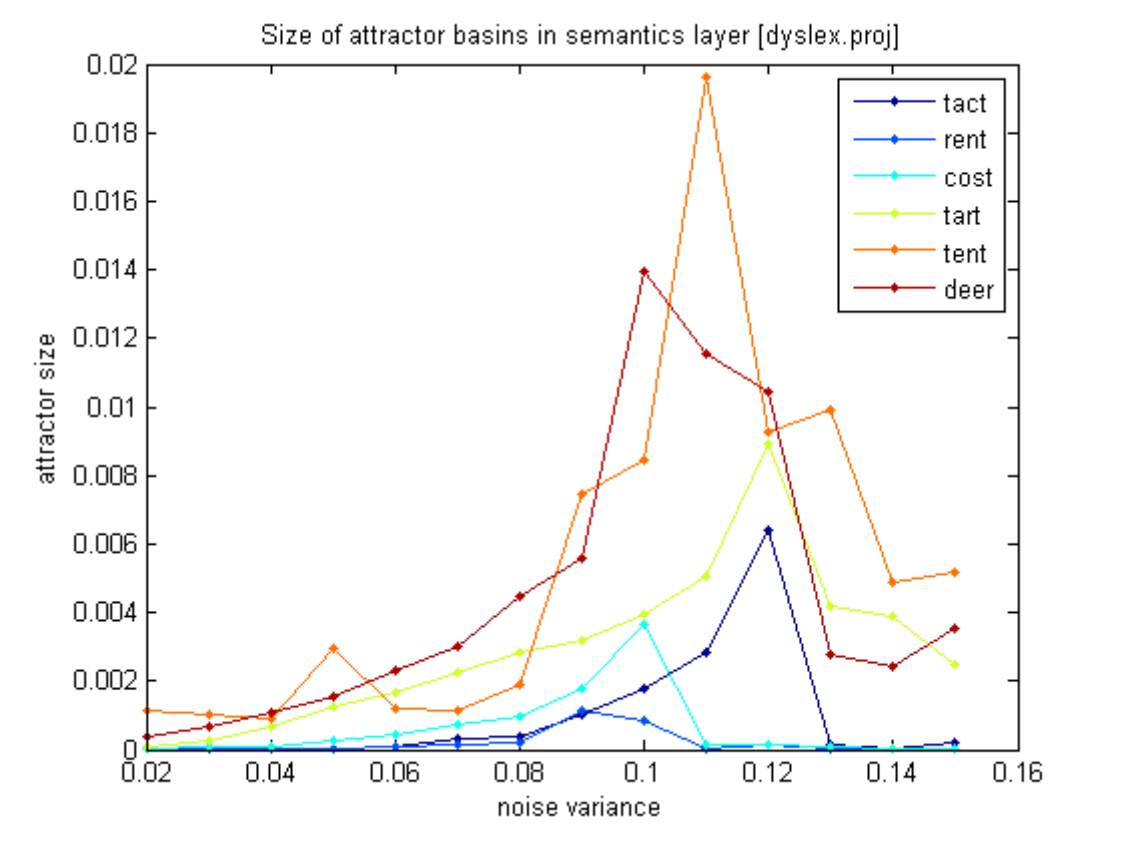


Attention is focused only for a brief time and than moved to the next attractor basin, some basins are visited for such a short time that no action may follow, no chance for other neuronal groups to synchronize. This corresponds to the feeling of confusion, not being conscious of fleeting thoughts.

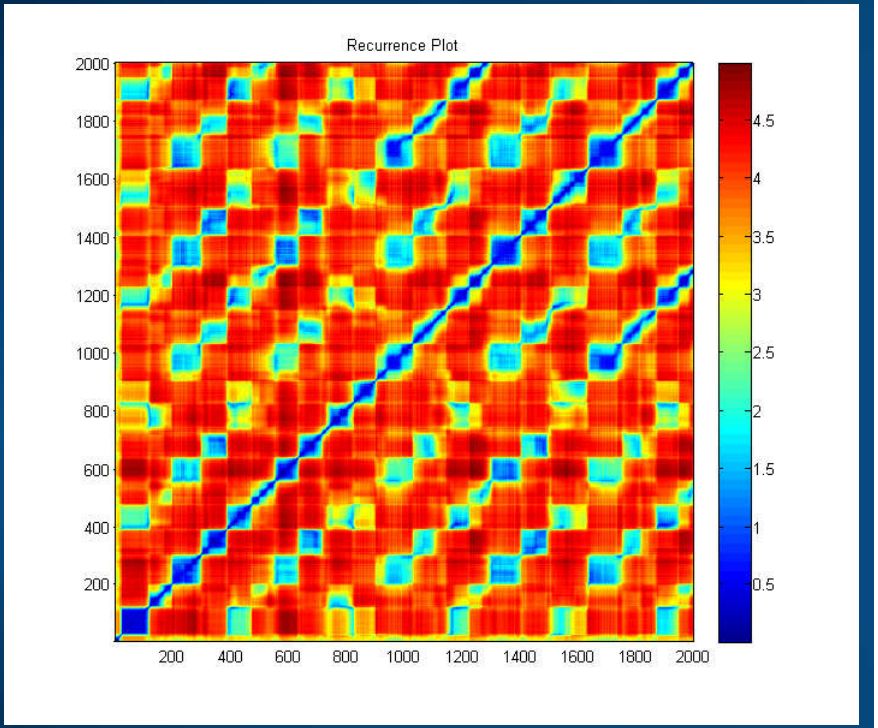
Depth of attractor basins

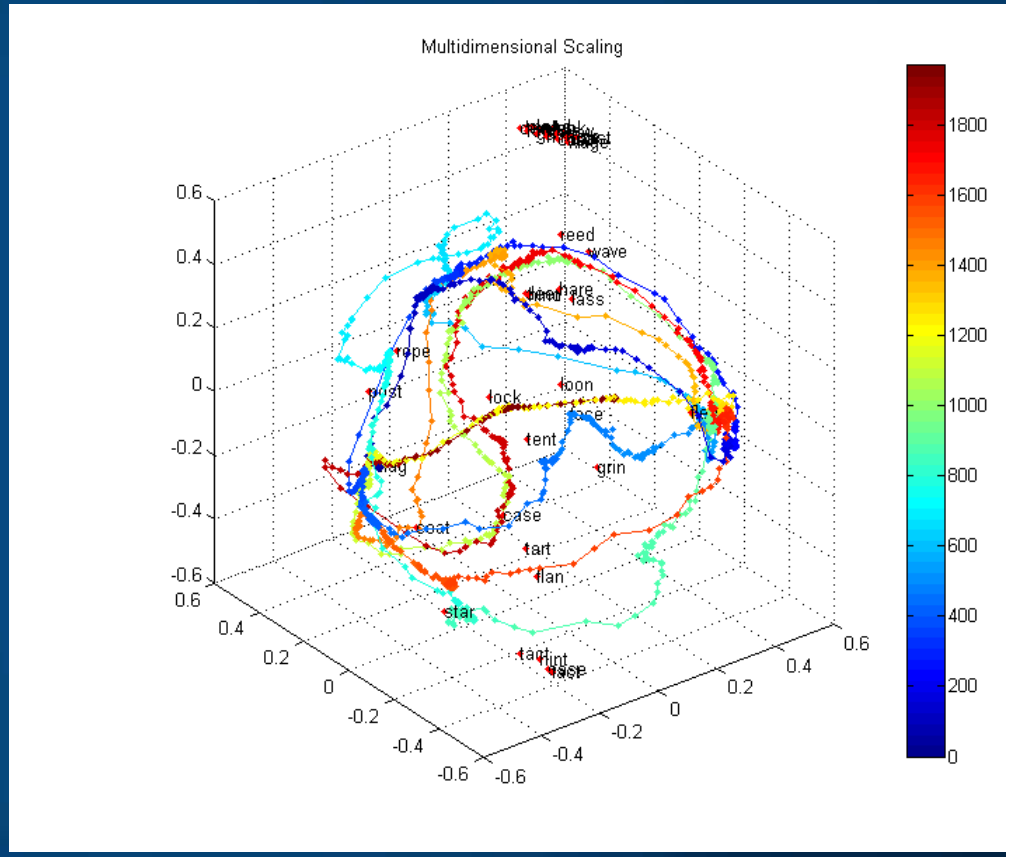
Variance around the center of a cluster grows with synaptic noise; for narrow and deep attractors it will grow slowly, but for wide basins it will grow fast.

Jumping out of the attractor basin reduces the variance due to mutual inhibition of all desynchronized neurons.

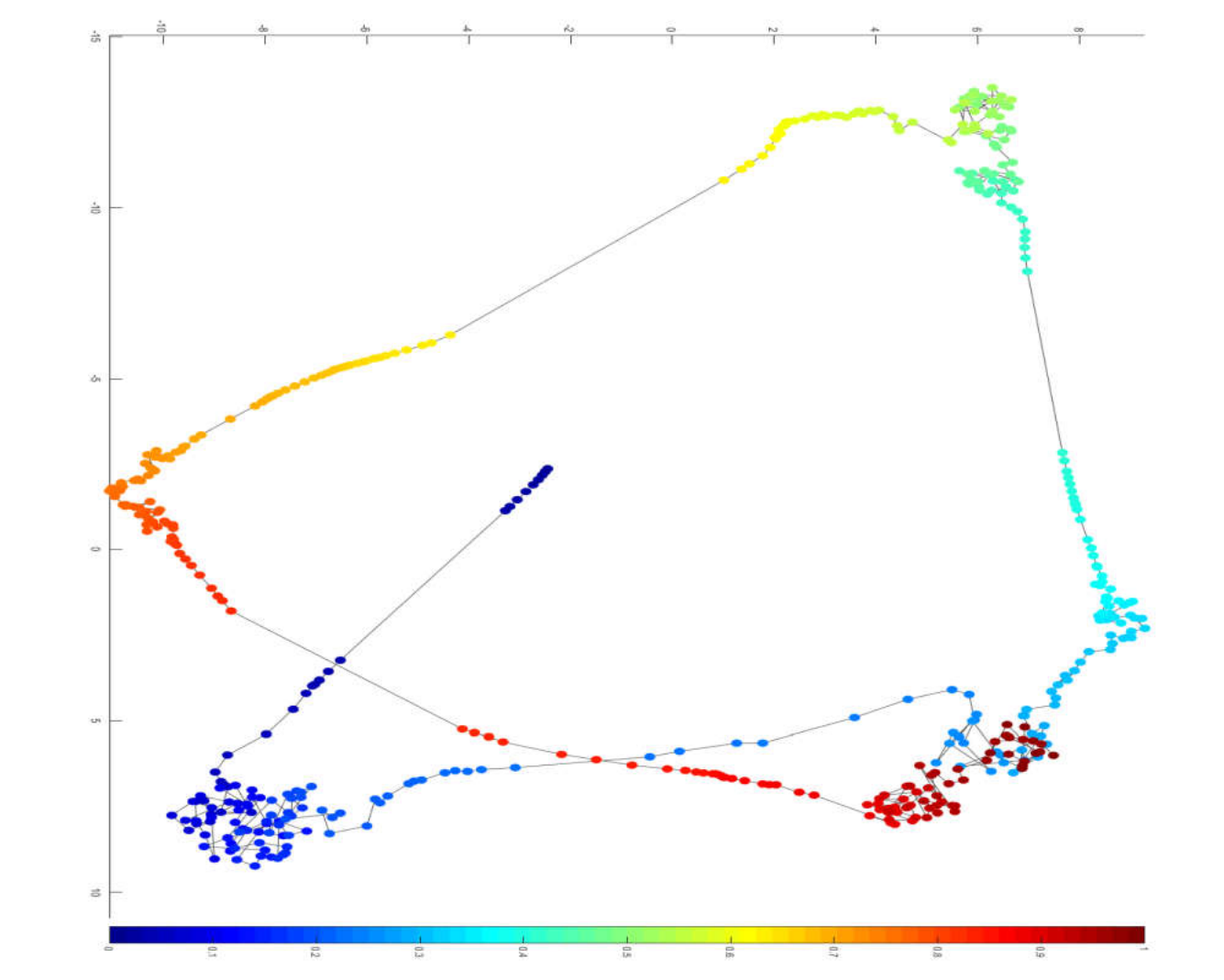


Long trajectories

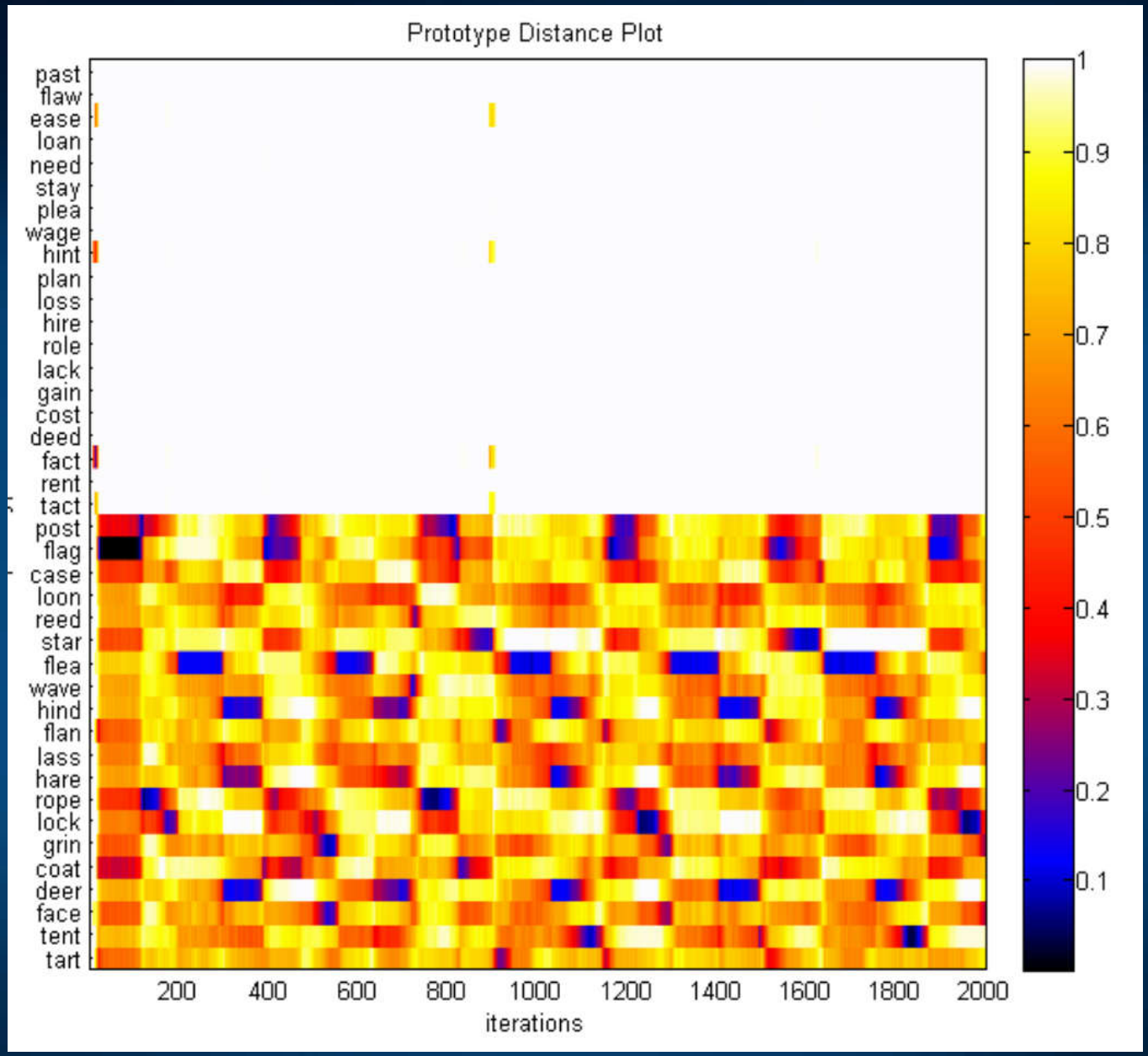




Recurrence plots vs MDS, starting with the word “flag” in 40-words microdomain, chain of mental states. You never step into the same river twice, each state is “dressed in history”.



Other options: Stochastic Neighbor Embedding (SNE) and faster t-SNE variants; MDS is more costly.

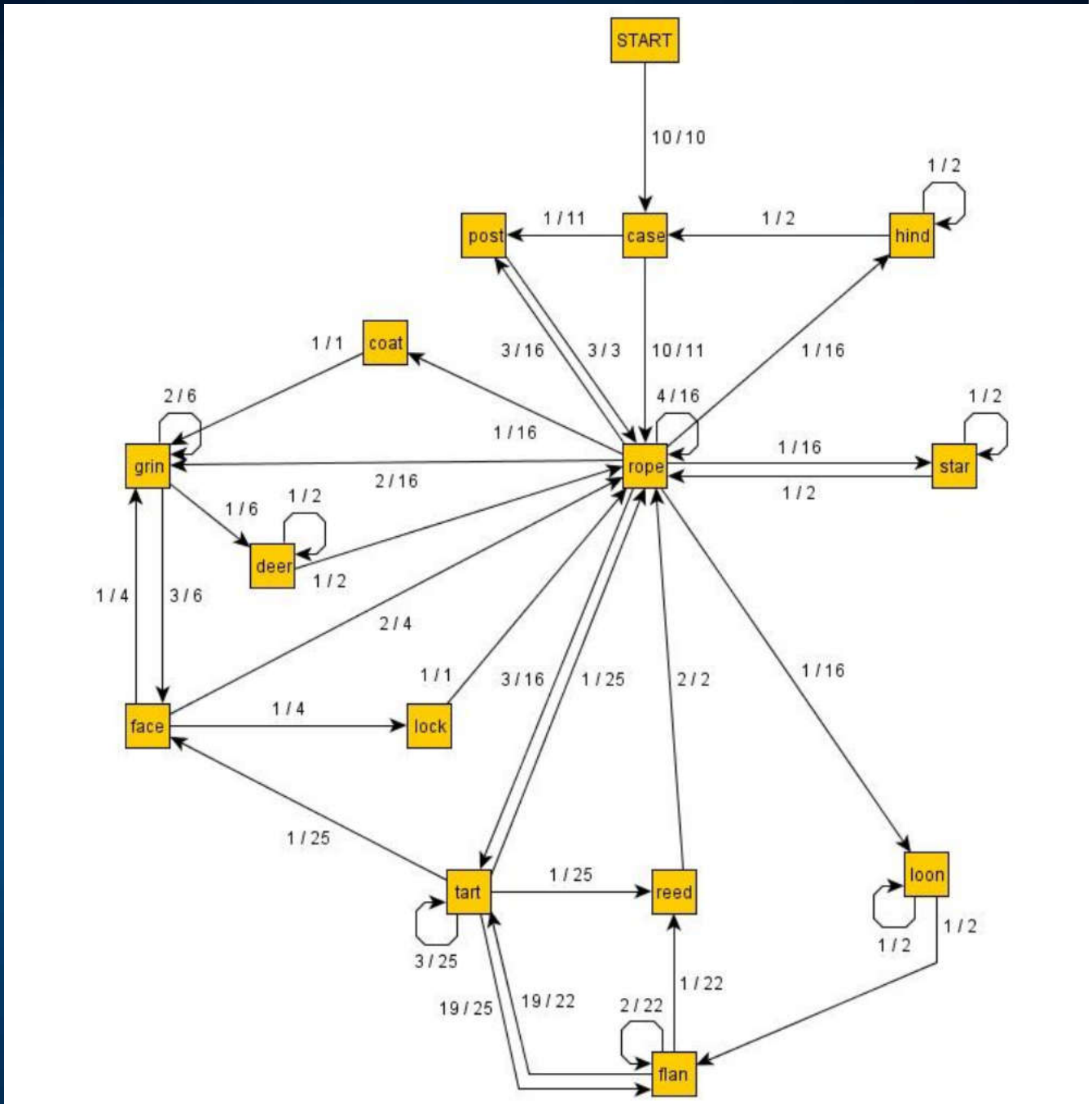


PDP shows how far is the current state from basins of attractors.
Abstract concepts have different set of microfeatures, not activated here.

Discretization showing transitions between attractors, 10 runs.

Why these particular transitions?

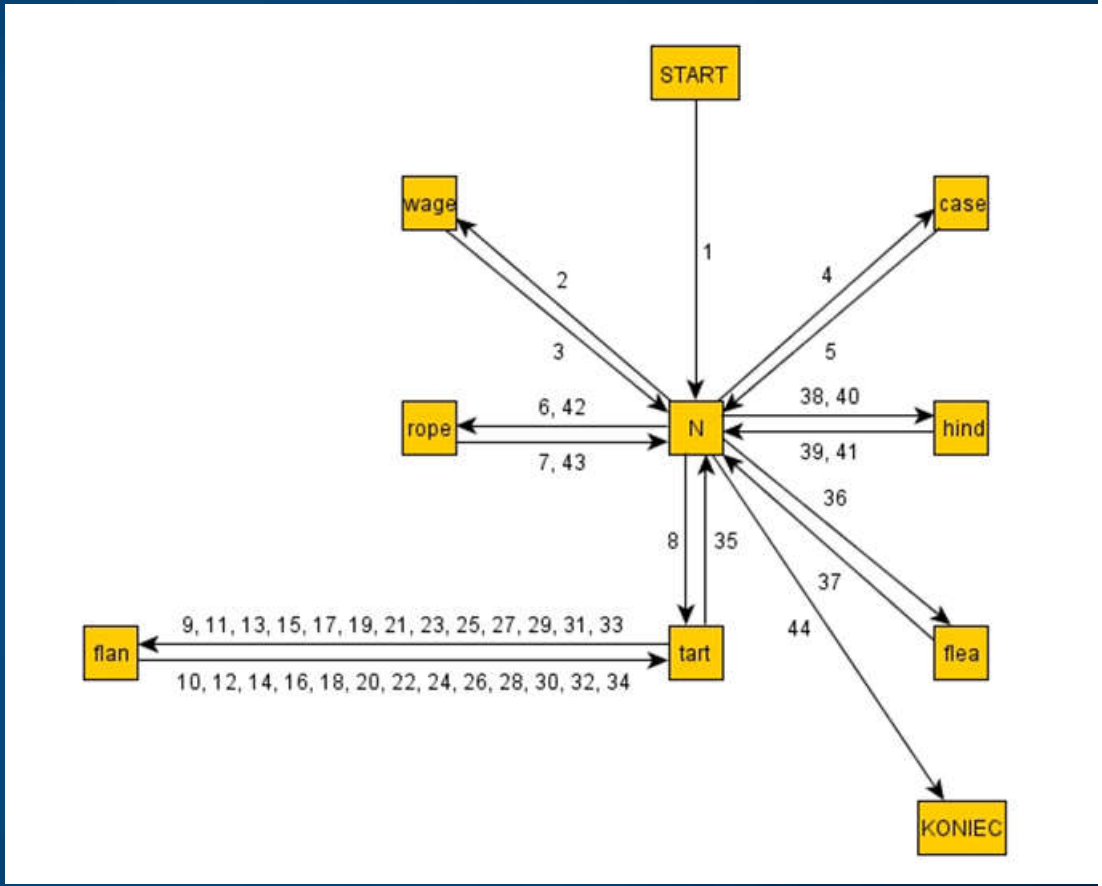
Connected attractors share some microfeatures, some are deactivated, but visualization using RP or FSD does not show such details.
In the phase space dimensions are rescaled during dynamics.



Transition graphs

Like in molecular dynamics, long time is needed to explore various potential transitions between attractor basins – depending on priming (previous dynamics or context) and noise in the system.

In some cases this model may get into obsessive kind of loop, like here, alternating between “tart” and “flan”.



MDS word mapping

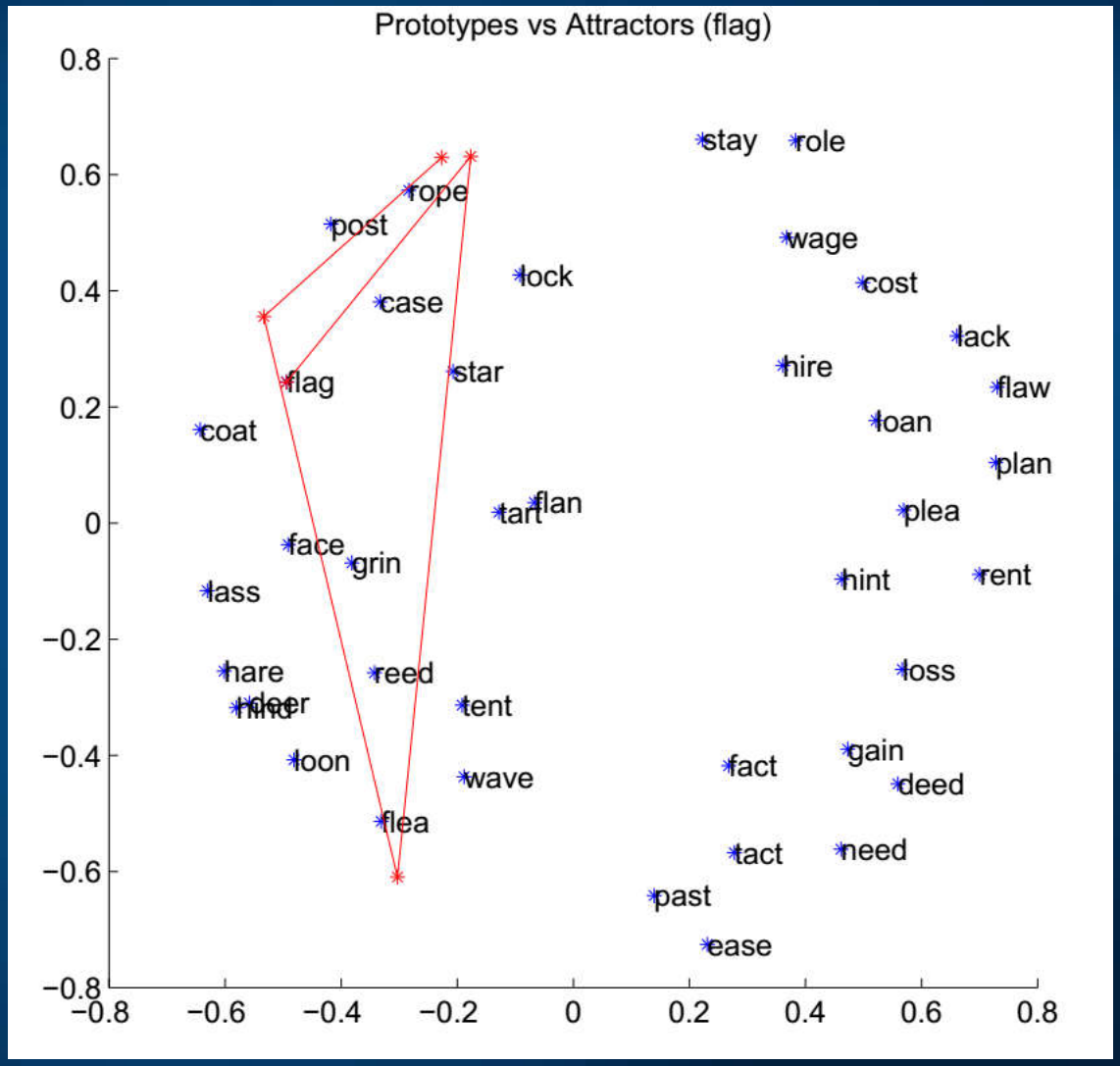
MDS representation of all 40 words, showing similarities of their 140 dimensional vectors.

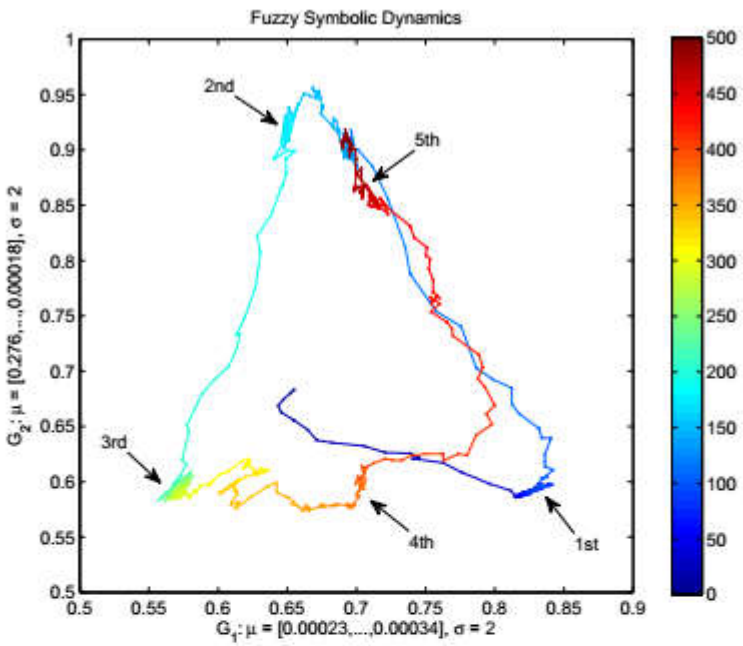
Attractors are in some cases far from words.

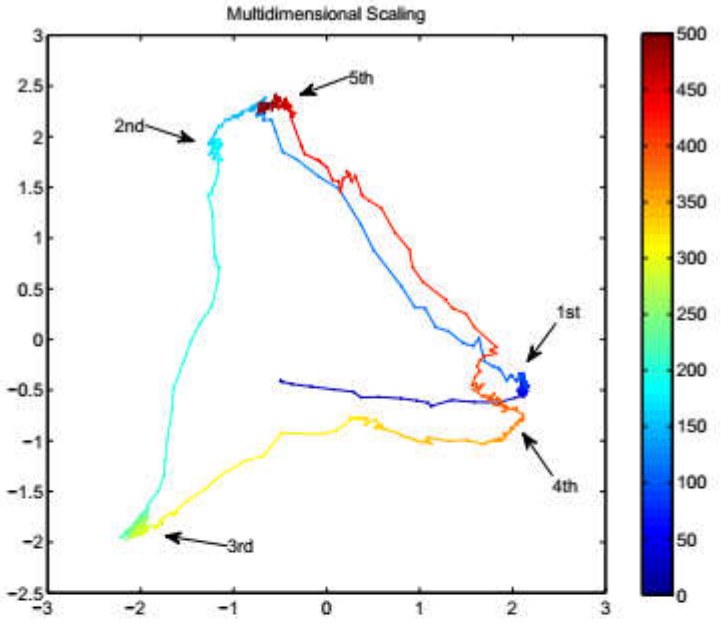
Transition

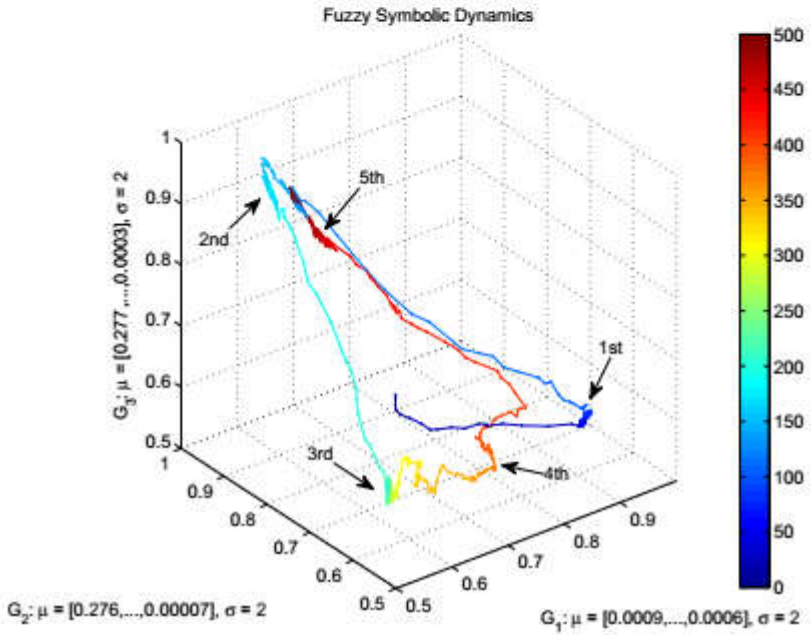
Flag => rope => flea,

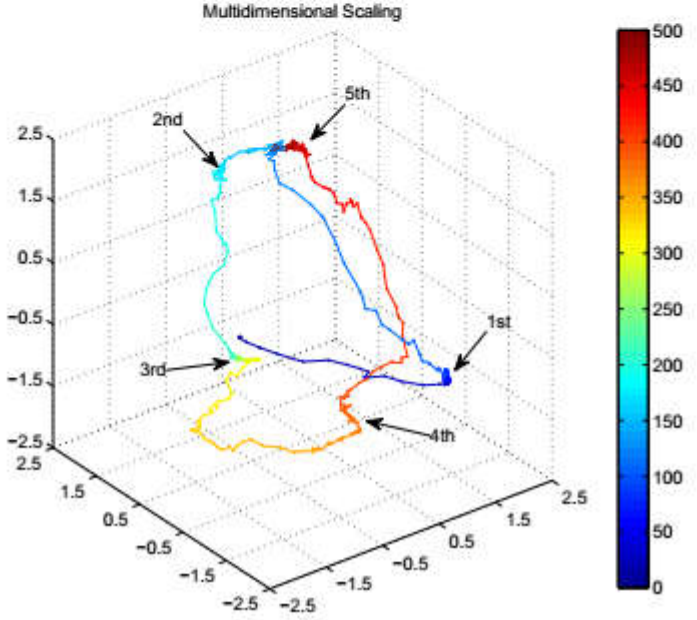
not clear why such big jump.




Fuzzy Symbolic Dynamics
2nd
5th
3rd
4th
1st
G_2: μ = [0.276,...,0.00018], σ = 2
G_1: μ = [0.00023,...,0.00034], σ = 2


Multidimensional Scaling
5th
2nd
1st
4th
3rd


Fuzzy Symbolic Dynamics
5th
2nd
1st
3rd
4th
G_3: μ = [0.277,...,0.0003], σ = 2
G_2: μ = [0.276,...,0.00007], σ = 2
G_1: μ = [0.0009,...,0.0006], σ = 2


Multidimensional Scaling
5th
2nd
1st
3rd
4th

Some questions

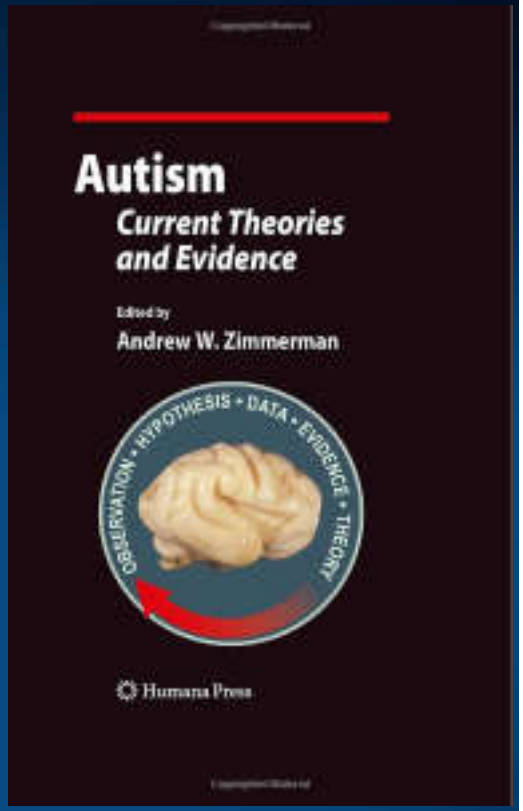
Stream of mental states = attractor states + transitions between them.

Problems:

1. Jumping between subspaces of different subsets of dimensions; rescaling dimensions? Manifold learning?
2. How to imagine multidimensional attractors? Trajectory has many “escape channels” requiring different energy.
3. Real EEG dynamics is oscillatory, how to transform it to attractor dynamics? First use source localization?
4. Distances (transition probabilities) in neural space are not symmetric – use Finsler spaces?
5. Natural Language Processing based on spreading activation in networks?
6. How to use attractor dynamics to construct mental models?

Emergent simulations and ASD+ADHD theory

Theories, theories



Best book on ASD so far:

- Andrew W. Zimmerman (Ed.)
  Autism; current theories and evidence.
  Humana Press 2008.

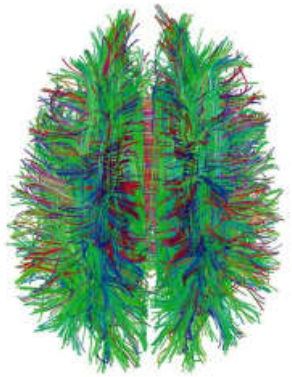
20 chapters divided into six sections:

- Molecular and Clinical Genetics (4 chapters);
- Neurotransmitters and Cell Signaling (3 chapters);
- Endocrinology, Growth, and Metabolism (4 chapters);
- Immunology, Maternal-Fetal Effects, and Neuroinflammation (4 chapters);
- Neuroanatomy, Imaging, and Neural Networks (3 chapters);
- Environmental Mechanisms and Models (2 chapters).

Other: Grossberg ART model. At which level can we understand not just correlations, but real mechanisms responsible for behavioral symptoms?

(genes, proteins, biochemistry, ion channels, synapses, membranes)
⇔ (neural properties, networks) ⇔ (behavior, syndromes, disease).

Reduced functional connectivity



The underconnectivity theory of autism is based on the following:

- Excess of low-level (sensory) processes.
- **Underfunctioning** of high-level neural connections and synchronization,
- fMRI and EEG study suggests that adults with ASD have local overconnectivity in the cortex and weak functional connections between the frontal lobe and the rest of the cortex.
- **Underconnectivity** is mainly within each hemisphere of the cortex and that autism is a disorder of the association cortex.
- Patterns of low function and aberrant activation in the brain differ depending on whether the brain is doing social or nonsocial tasks.
- "**Default brain network**" involves a large-scale brain network (cingulate cortex, mPFC, lateral PC), shows low activity for goal-related actions; it is active in social and emotional processing, mindwandering, daydreaming.
- Activity of the default network is negatively correlated with the "action network" (conscious goal-directed thinking), but this is not the case in autism – perhaps disturbance of self-referential thought?

Why? Genetics? Lack of sufficiently frequent internal stimulations?

Reduced fun

The underconnectivity theory

- Excess of low-level (senso
- **Underfunctioning** of high-
- fMRI and EEG study sugge
  overconnectivity in the co
  the frontal lobe and the re
- **Underconnectivity** is mai
  that autism is a disorder o
- Patterns of low function a
  depending on whether the
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  active in social and emotic
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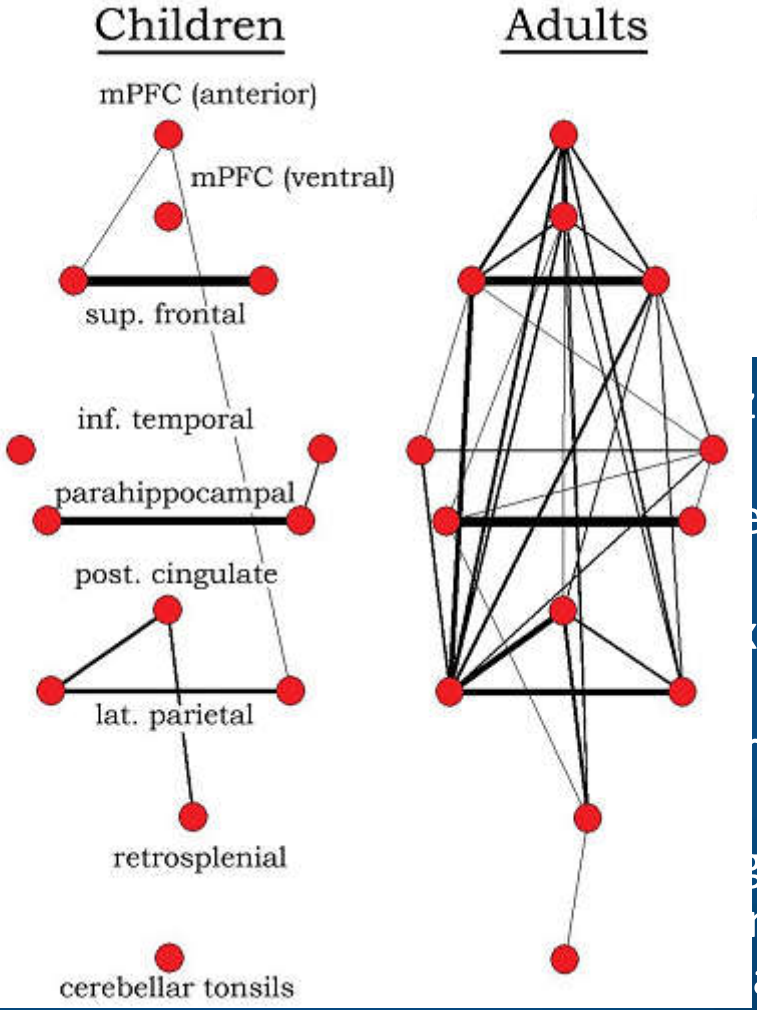

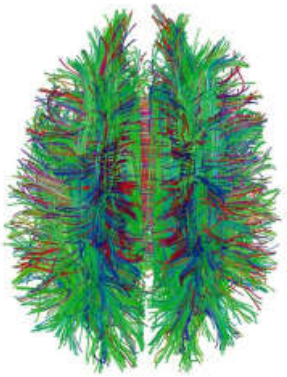

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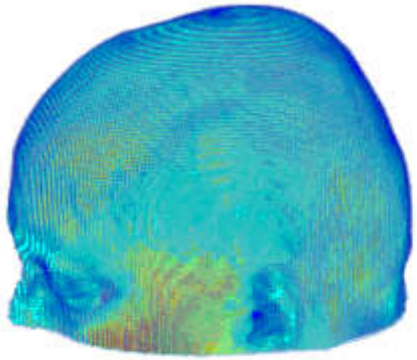
Why? Genetics? Lack of sufficiently frequent internal stimulations?

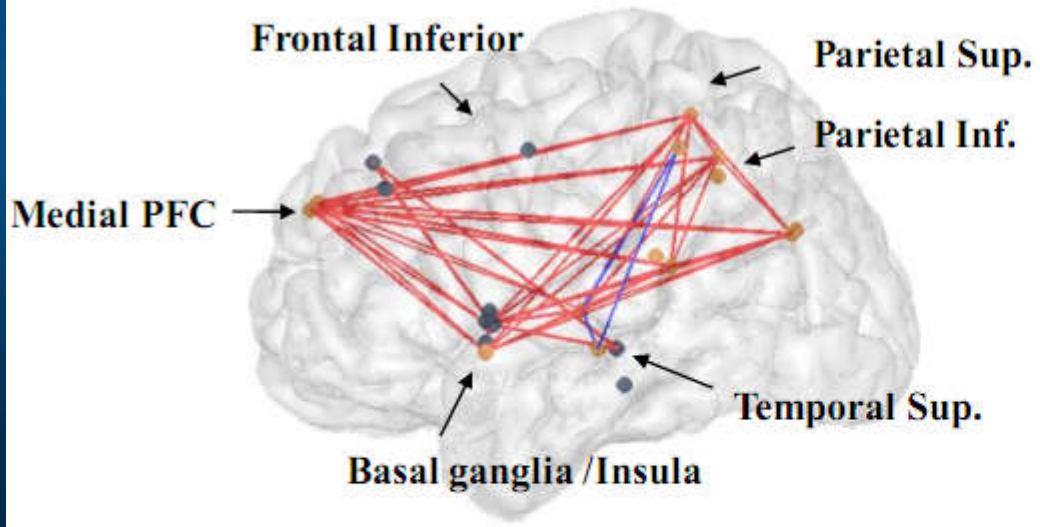
Head position



Connectivity : 63 ROI analysis

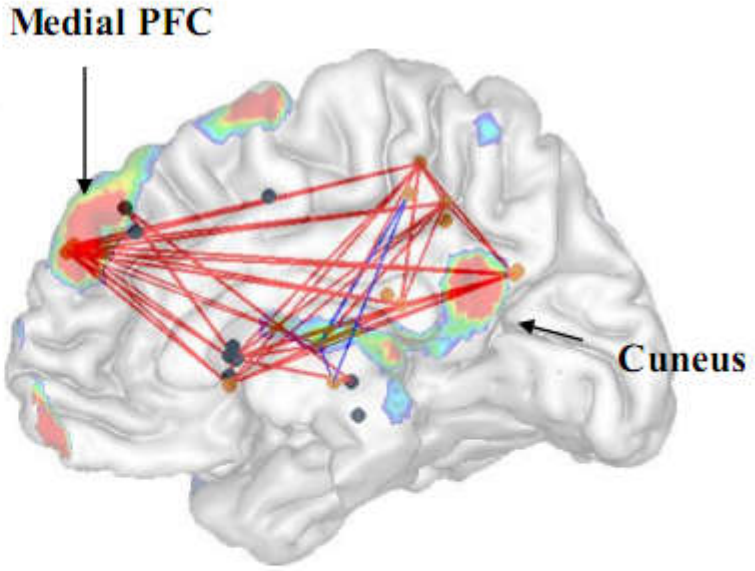
Significant in ASD not in Controls

Significant in Controls, not in ASD



Region of the default mode network

Region of the active network

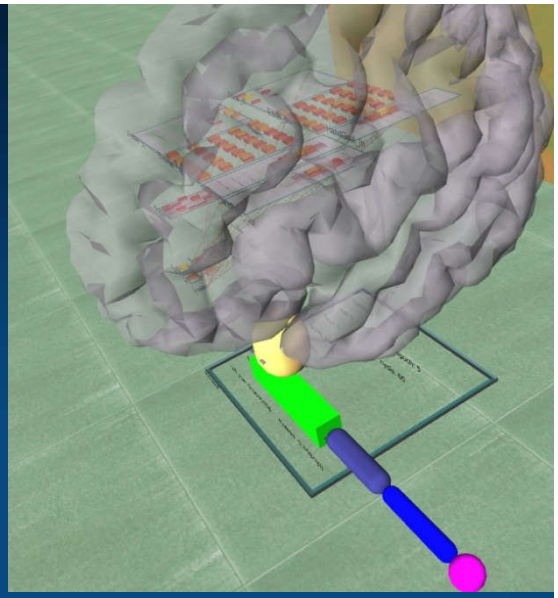


Brain activations in the FMRI experiment on emotion perception

Emergent:

Emergent is a powerful tool for simulation of biologically plausible, complex neural networks:

http://grey.colorado.edu/emergent



Simulating the brain functions

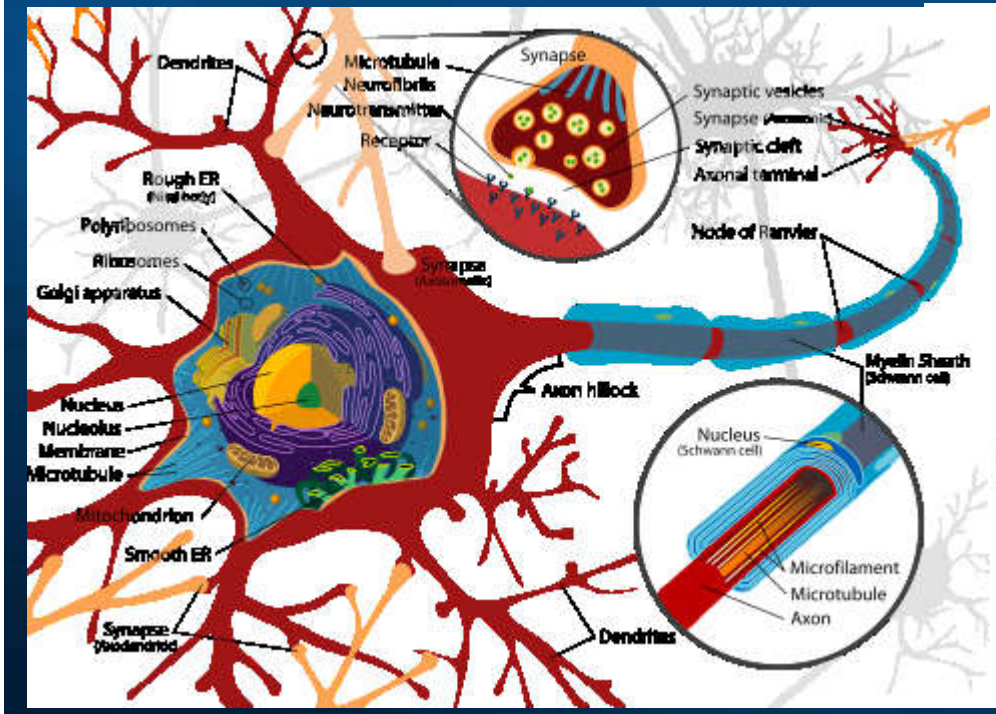
Emergent supports:

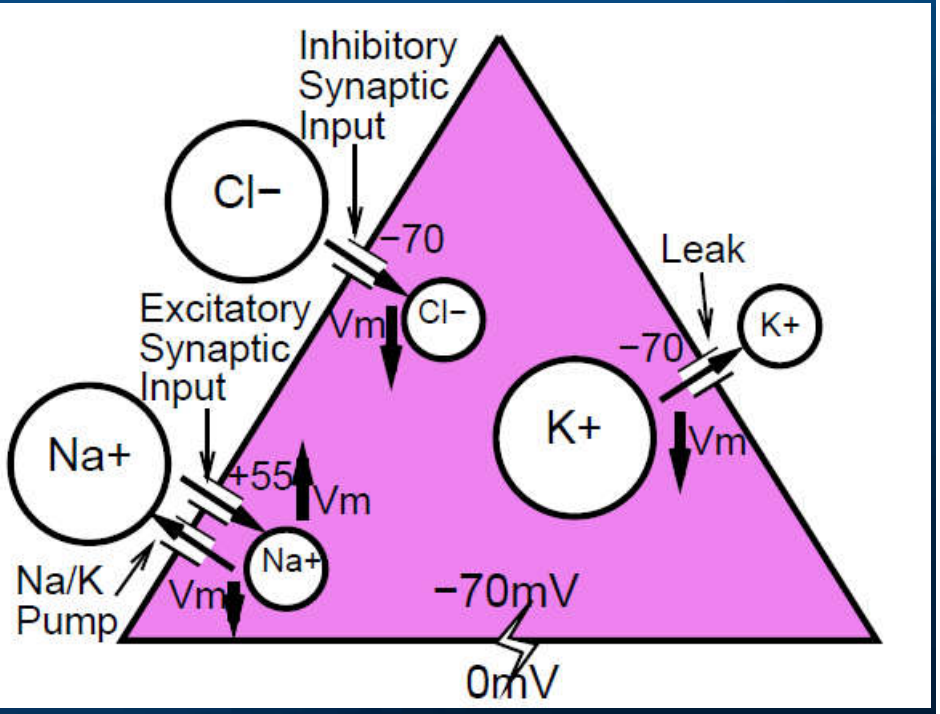
- Classic back-propagation and recurrent back-propagation and variants,
- Constraint-satisfaction (CS) including the Boltzmann Machine, Interactive Activation and Competition, and other related algorithms;
- Self-organized learning including Hebbian Competitive learning and variants, with Kohonen's Self-Organizing Maps and variants
- Leabra (``local error-driven and biologically realistic algorithm'')
- Real Time Neural Simulator
- Long Short Term Memory
- Oscillating Inhibition Learning Mechanism

Neuron or abstraction?

Neurons are very complex biological cells.

Simplest description that preserves some interesting biophysical properties treats them as point objects (no geometrical parameters) that can be charged by positive ions (excitatory input) flowing through ion channels in membranes and synapses.

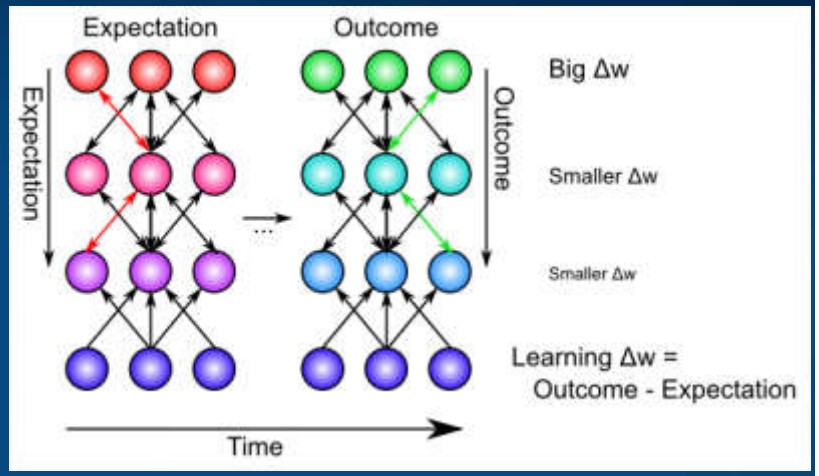




Hebb + error correction

Both approaches are needed:

$$\Delta w_{ij} \approx \Delta_{hebb} + \Delta_{err}$$



Correlation learning and error terms:

$$\Delta_{hebb} = \varepsilon\left(x_i - w_{ij}\right) y_j$$

$$\Delta_{err} = \varepsilon\left(x_i^+ y_j^+ - x_i^- y_j^-\right)$$

– and + phases, expectations and feedbacks, alternate quickly, ~ 0.1 sec.

Weighted combination

$$\Delta w_{ij} = (k_{hebb})\Delta_{hebb} + (1 - k_{hebb})(\Delta_{err})$$

kWTA implements inhibition inside layers, creating sparse internal representations. Neurons compete with each other and only the best neurons, specializing in a given task and only the most confident (i.e. highly active), are left.

Combo properties

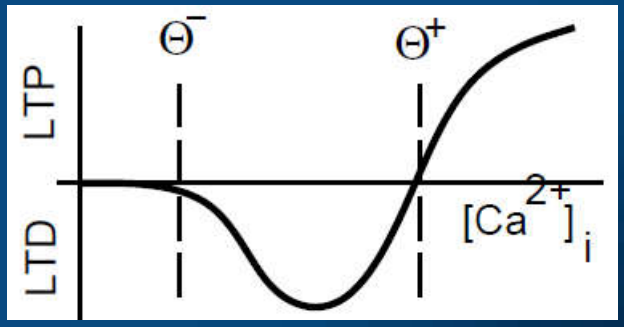
Hebbian learning creates a model of basic features of the world, correlations between events and features but is not able to learn heteroasscociations.

Hidden layers allow for transformation of data into different feature space while error correction learns arbitrary input-output relations (behaviors).

Combined Hebbian correlation learning ($x_i \sim y_j$) and error correction learning should be able to learn everything in a biologically plausible way.

Connections in the brain are bidirectional.

Biology: no Ca^{2+} = no learning;
little Ca^{2+} = LTD,
a lot of Ca^{2+} = LTP.



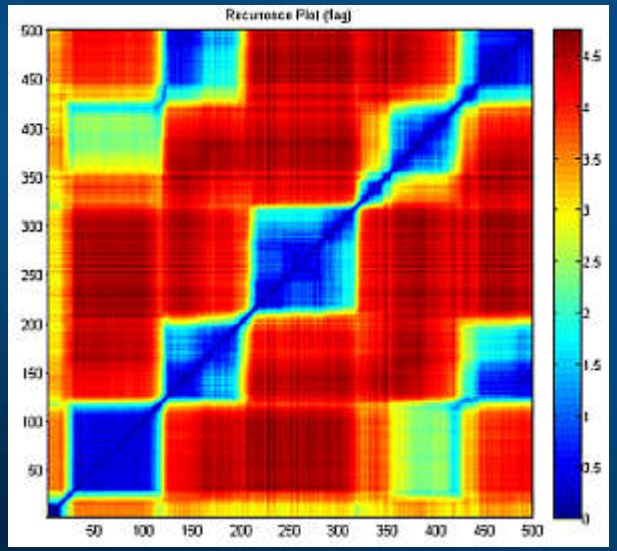
$$\Delta w_{ij} = \epsilon[(x_i^+ y_j^+) - (x_i^- y_j^-)]$$

\+ = LTP, – =LTD in the table,
LTD = unfulfilled expectations,
only the – phase without enhancement from the + or outcome phase.

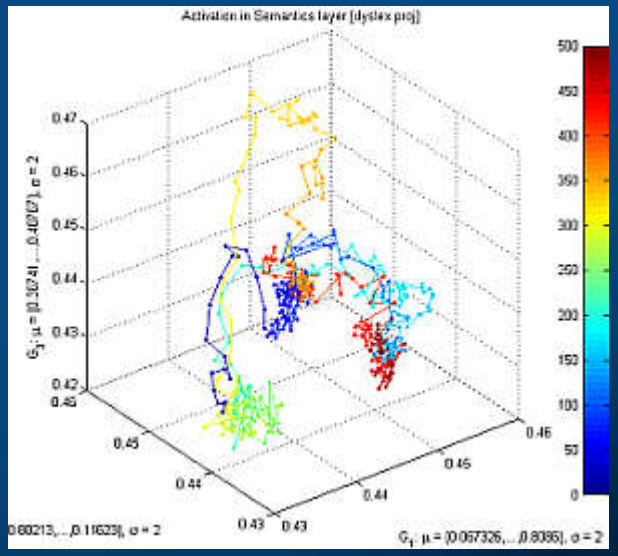
	Plus Phase					
	$x_i^+ \; y_j^+ \approx 0$			$x_i^+ \; y_j^+ \approx 1$		
Minus Phase	Err	Hebb	Combo	Err	Hebb	Combo
$x_i^- \; y_j^- \approx 0$	0	0	**0**	+	+	**+**
$x_i^- \; y_j^- \approx 1$	–	0	**–**	0	+	**+**

Multiple constraint satisfaction

- Bidirectional connectivity leads to an **attractor dynamics,** or **multiple constraint satisfaction**: the network can start off in many initial states (the region called basin of attractor) and evolve towards specific attractor or prototype state, representing cleaned-up, stable interpretation of a noisy or ambiguous input pattern.
- This state is a compromise between multiple constraints, minimizing overall energy of the system.



Color = distance from the point at a given time shown on x, y axis.



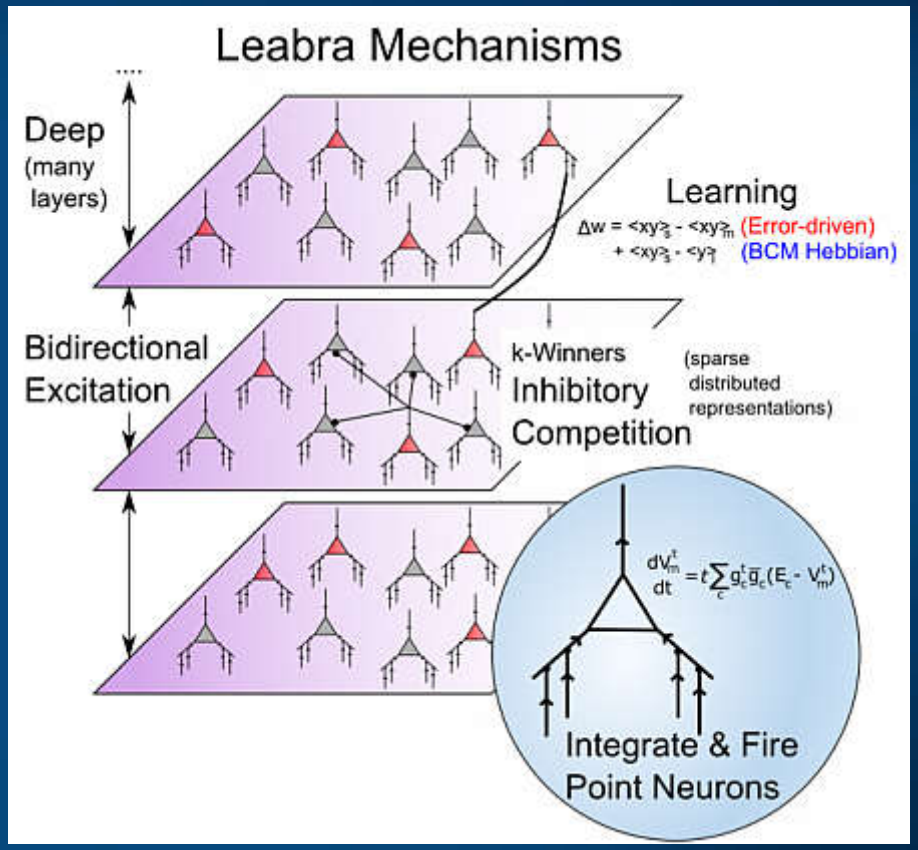
Color = time, several attractors for words, fast transitions; axis (x,y,x) = position.

Attractor dynamics is best visualized using recurrence plots or using Fuzzy Symbolic Dynamics technique to see high-dimensional trajectories.

Leabra learning model

Leabra =
Learning in an Error-driven and Associative, Biologically Realistic Algorithm

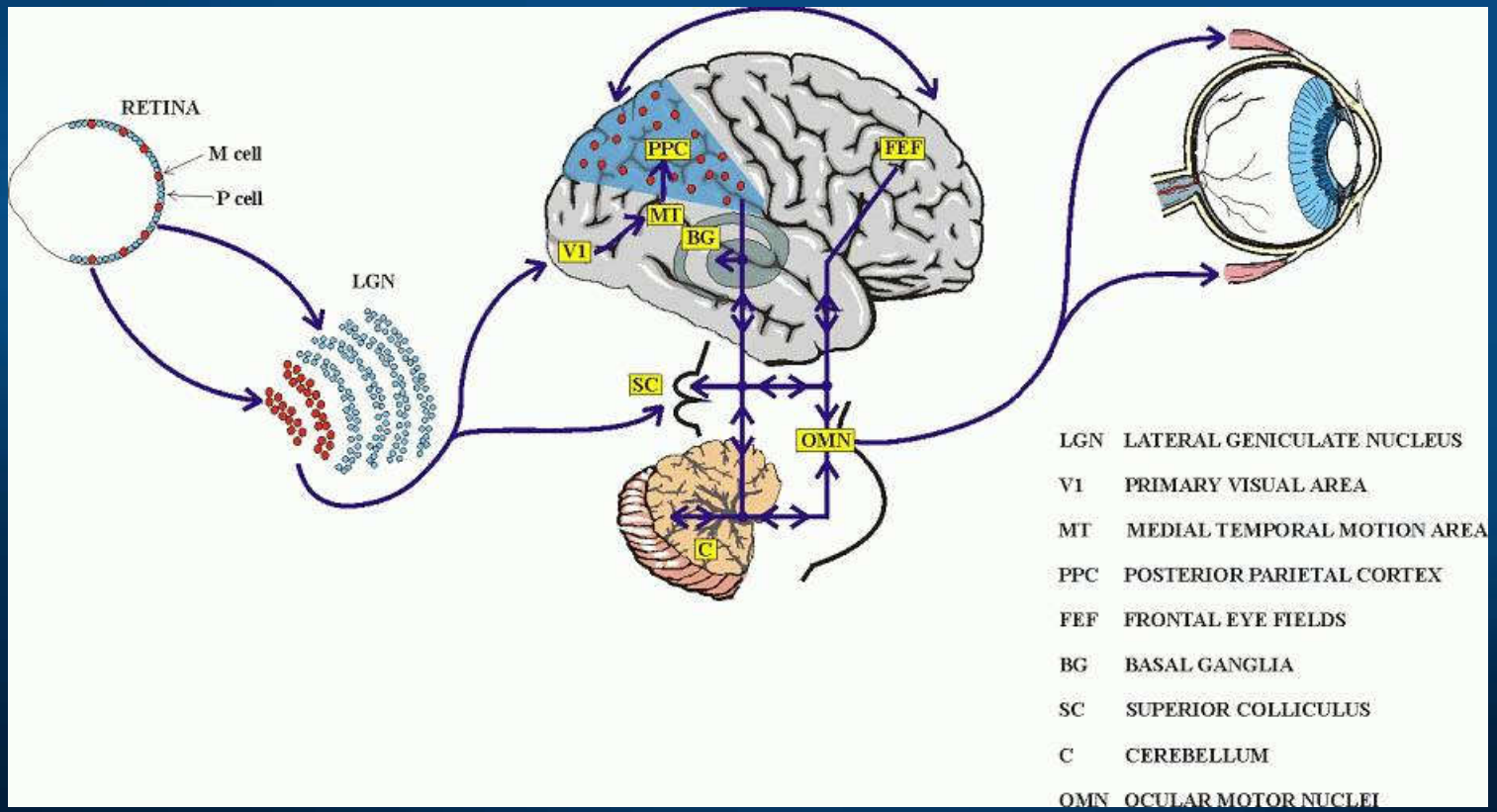
So far we are discussing only how local learning is possible, but all this has to be embedded in overall cognitive architecture.



6 principles embedded in Leabra:
integrate & fire point neurons, kWTA, sparse distributed representations, many layers of transformation, Hebb & error correction learning.

Vision

From retina through lateral geniculate body, LGN (part of thalamus) information passes to the primary visual cortex V1 and then splits into the ventral and dorsal streams.



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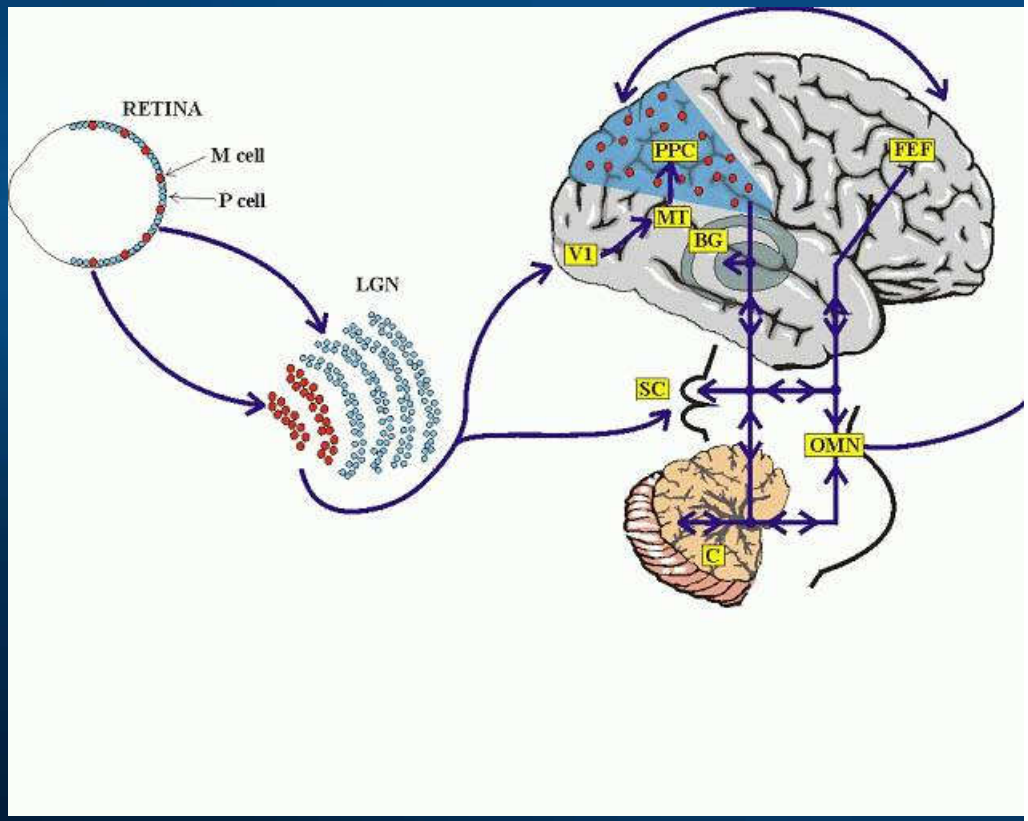
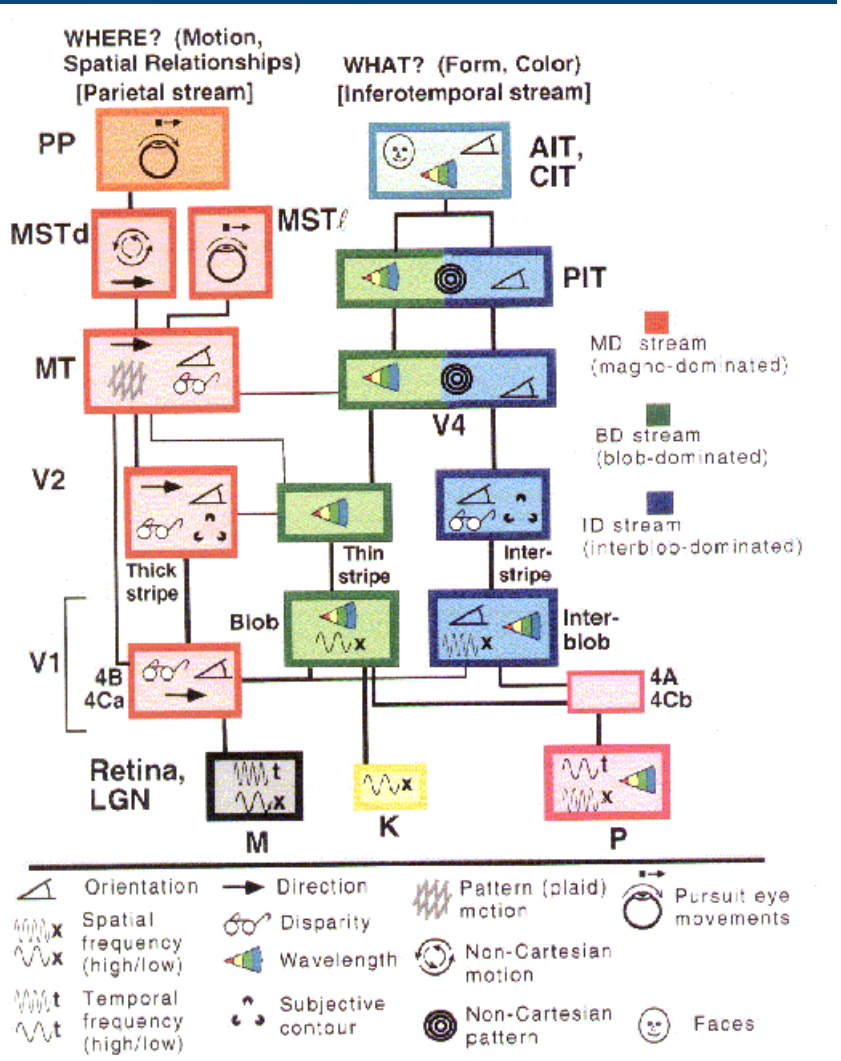
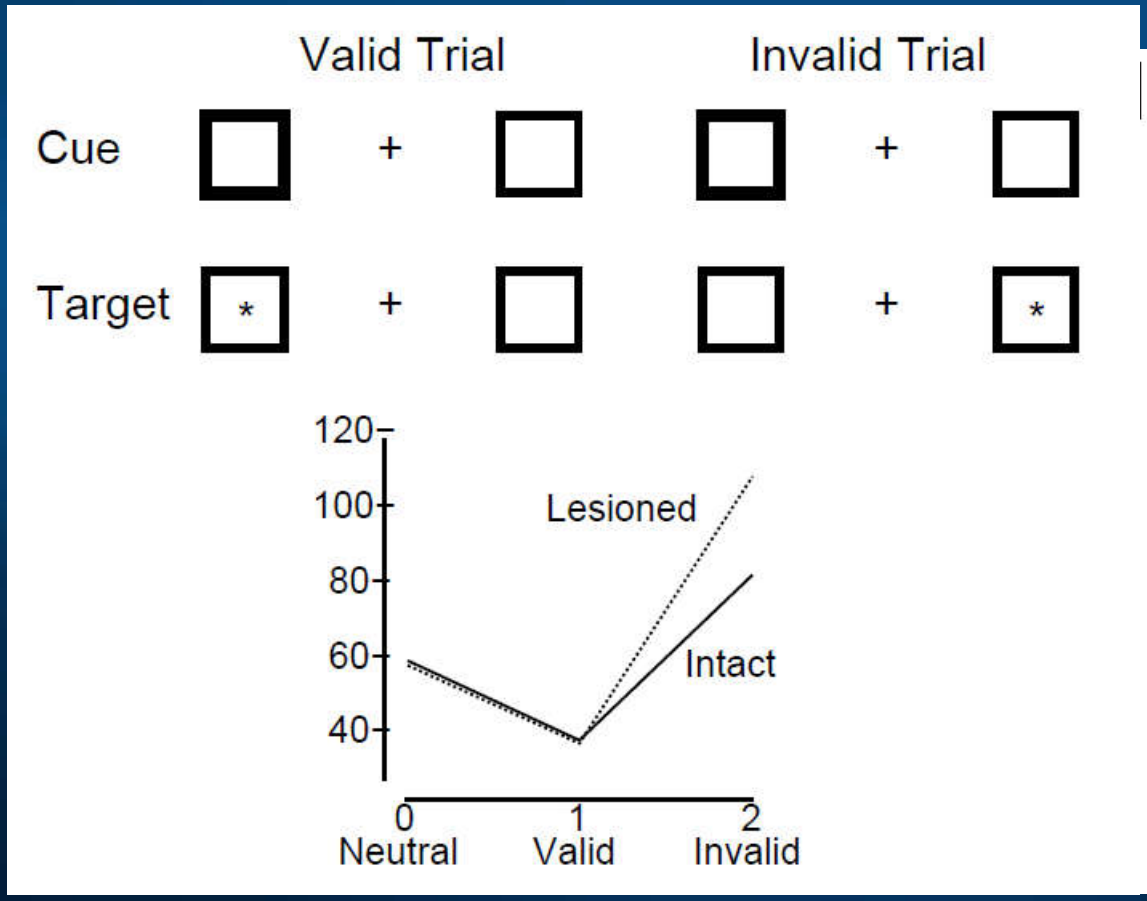


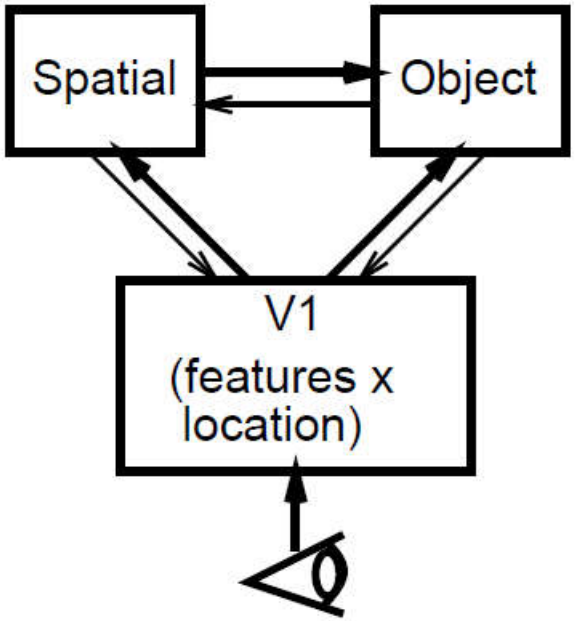


Posner visual orientation task

Cue (bright box) is in the same position as target (valid trial), or in another position (invalid trial), or there is no cue (neutral), just target.

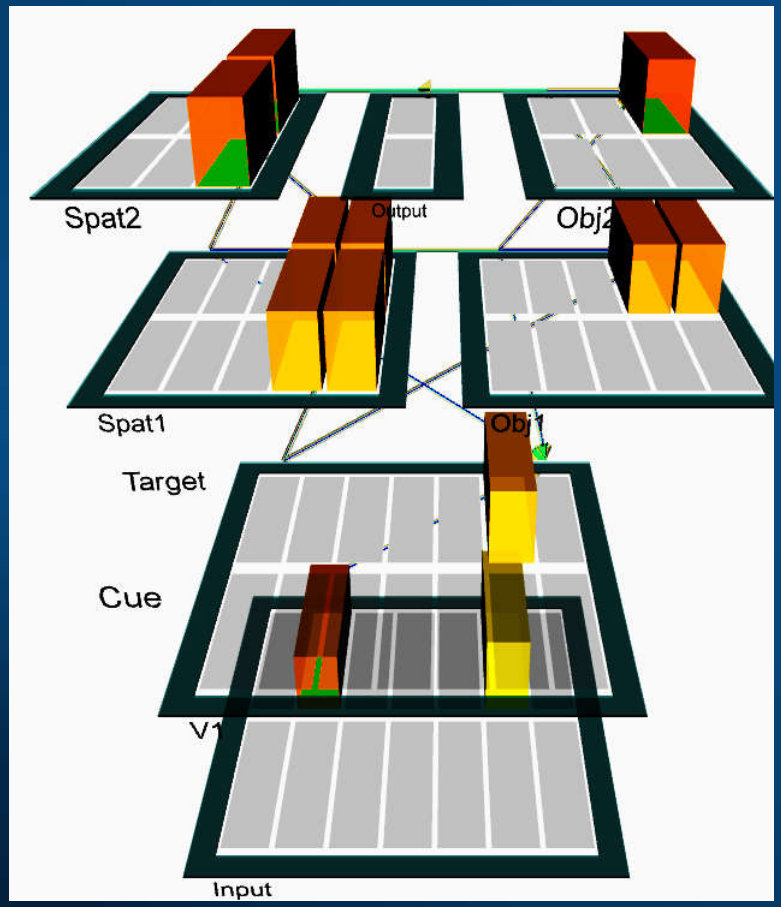
Test of the object recognition/localization.



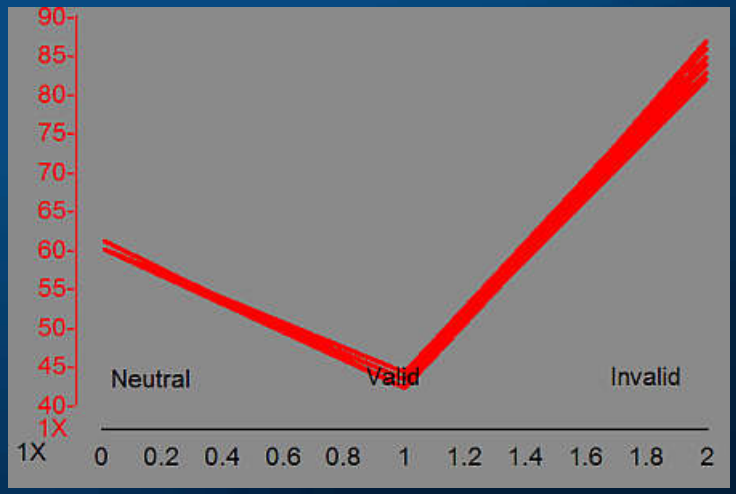


Posner spatial attention

Cue (bright box) is in the same position as target (valid trial), or in another position (invalid trial), or there is no cue (neutral).



Group	Name	Input
Neutral	Target	
Valid	Cue	
Valid	Target	
Invalid	Cue	
Invalid	Target	

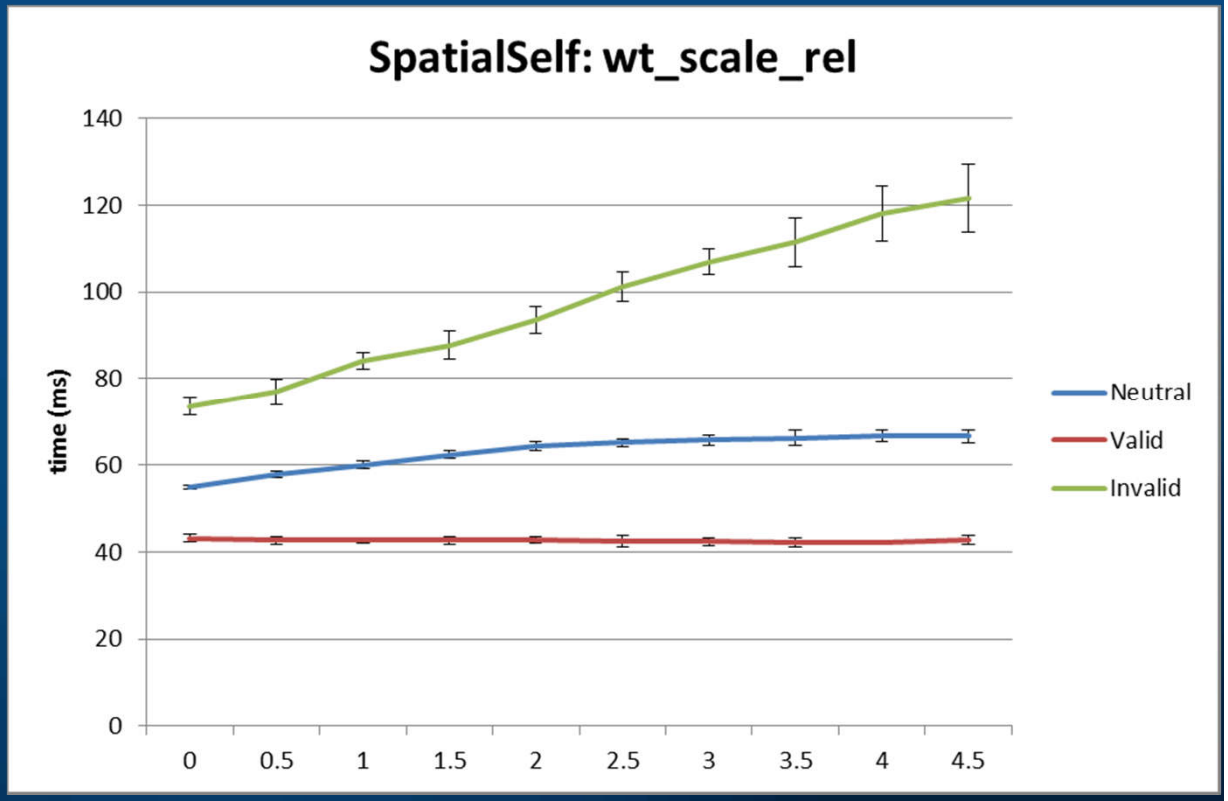


Posner: recurrence in Spat

Relative strength of recurrent connections in Spat1 and Spat2 layers has no influence on valid trials, weak influence on neutral, but stronger local connections significantly increase reaction times of invalid trials.

This mechanism may also contribute to long delays in shifts of attention.

TSC gene can cause local over-connectivity in the sensory cortices (visual, auditory) reducing normal neuronal pruning.



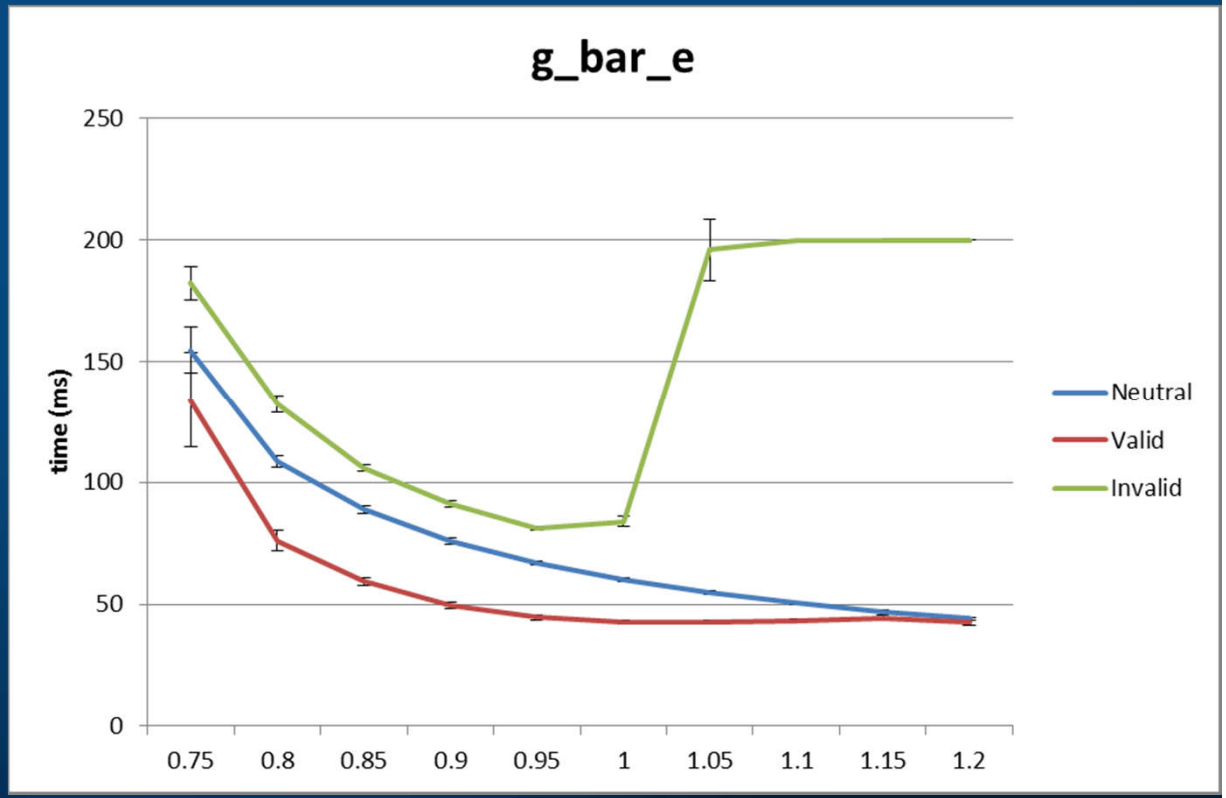
Posner: excitation/inhibition

Increase of maximal conductance for excitatory channels (mostly glutamatergic synaptic sodium channels) above 1 leads to sharp two-fold increase in invalid trial reaction times, and small decrease of the normal/valid trials reaction times;

decrease of this parameter slows down reaction times but keeps the differences roughly constant.

Increasing maximal conductance for inhibitory channels quickly increases the invalid trials reaction times without much change in results for other trials;

decrease has relatively small effect.

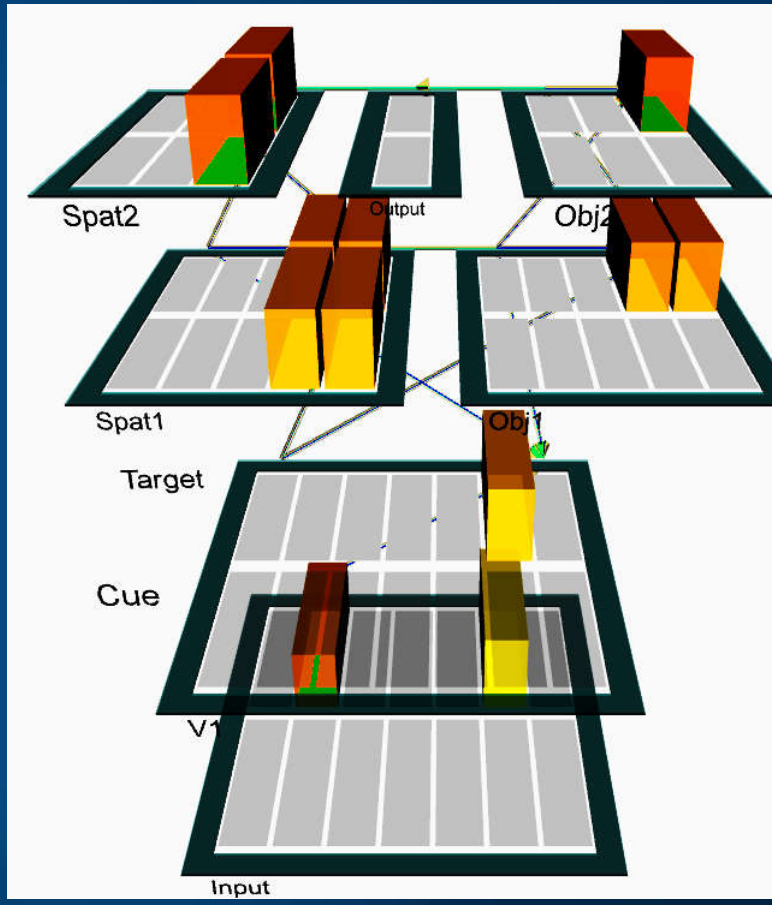


Posner: accommodation

Self-regulatory dynamics of neurons depends on complex processes, changing conductance of the ion channels (voltage-dependent gates).

Changing time constants for increases in intracellular calcium that builds up slowly as function of activation in all neurons has big influence on all reaction times, reducing the difference between all types of trials to zero and making reactions for valid trials slower than for invalid and neutral.

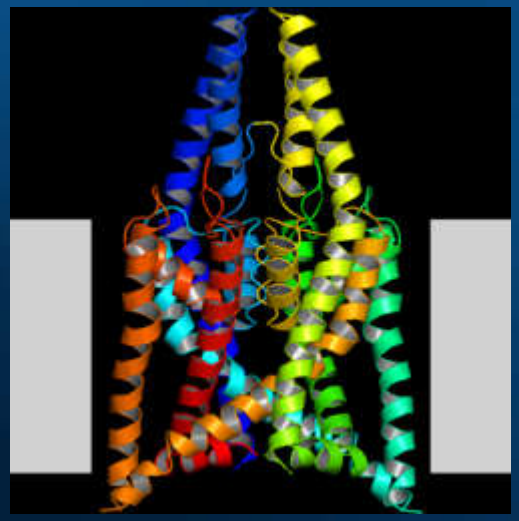
These processes depend on many types of ion channels and thus many genes are implicated.

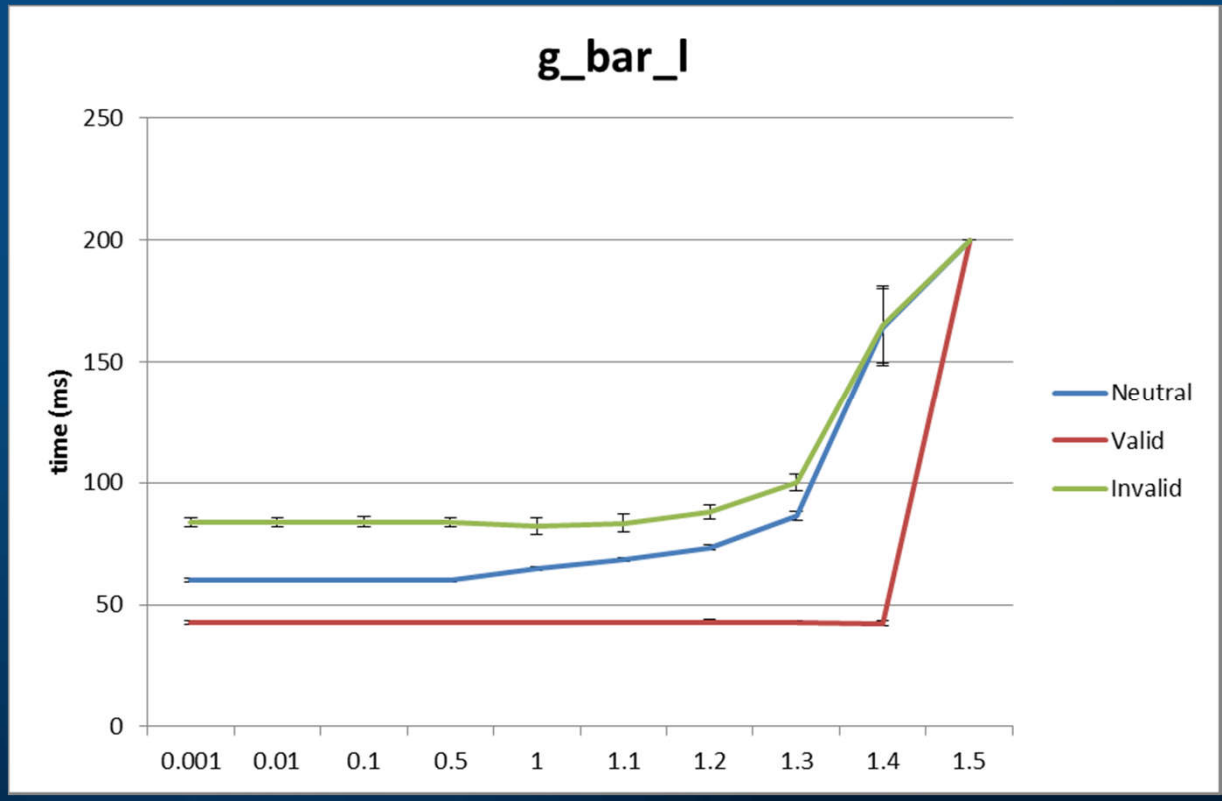


Posner: leak channels

Parameter regulating maximal conductance of leak (potassium K^+) channels changed from 0.001 to 1.3 has relatively small influence on reaction times. Beyond this value all reaction times become much longer.

Strong leak currents decrease membrane potentials and activation of neurons takes longer time. The KCNK gene family proteins build two-pore-domain potassium leak channels, the main suspect in this case.





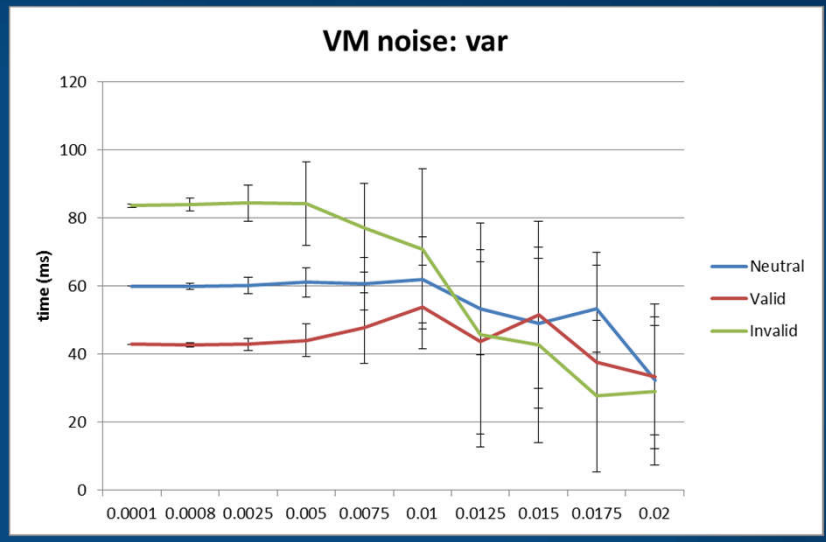
Posner: noise

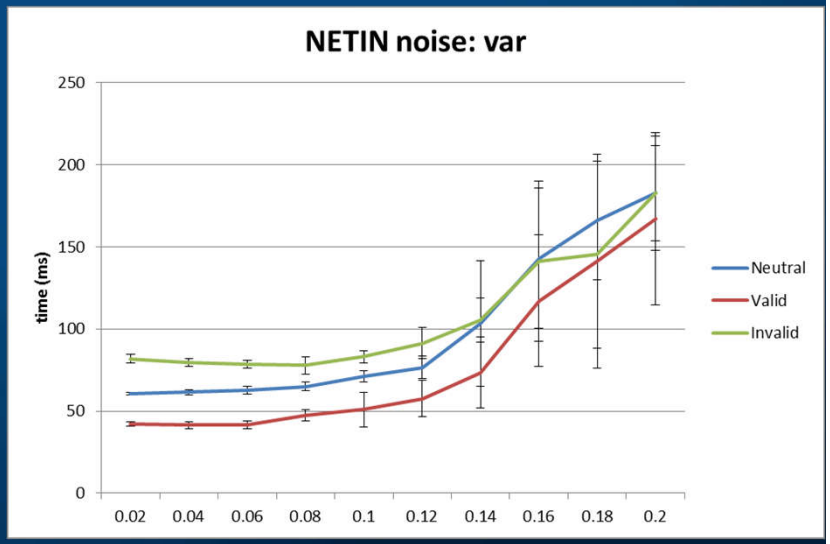
Noise may be included either as the variance of the value of membrane potential, or variance of the synaptic input.

The first type of noise makes the switch from invalid cue to the target position faster, decreasing sharply the time for invalid trials and to a smaller degree also other times.

Attractors become weaker and transitions may be made faster.

Synaptic noise has the opposite effect, competition between competing patterns becomes stronger and achieving the threshold for decision takes longer.
High density of synapses will contribute to the “synaptic bombardment” type of noise.

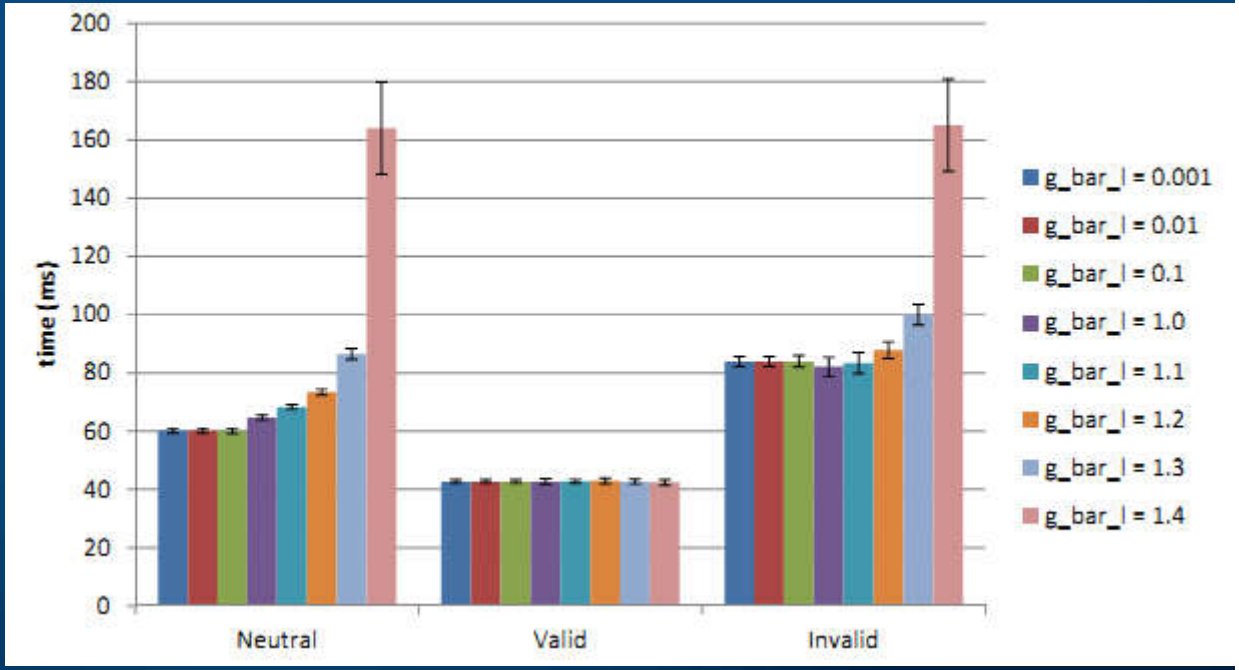




Posner spatial attention

- More complex cue = stronger local attractor => can bind ASD longer?
- Cue pulsating with different frequencies may create resonances?
- What changes in the network will lead to faster attention shifts?
- Broadening of attractor basins => helps to decrease symptoms?

- Diagnostic value?
- Explains fever effects?
- Suggest pharmacotherapy?
- Need for more accurate models.
- Model in GENESIS is inconclusive.



Spatial attention shifts in Posner experiments as a function of leak channel conductance change between 20-120 ms.

Recognition of many objects

- Vision model including LGN, V1, V2, V4/IT, V5/MT

Two objects are presented.

Connectivity of these layers:

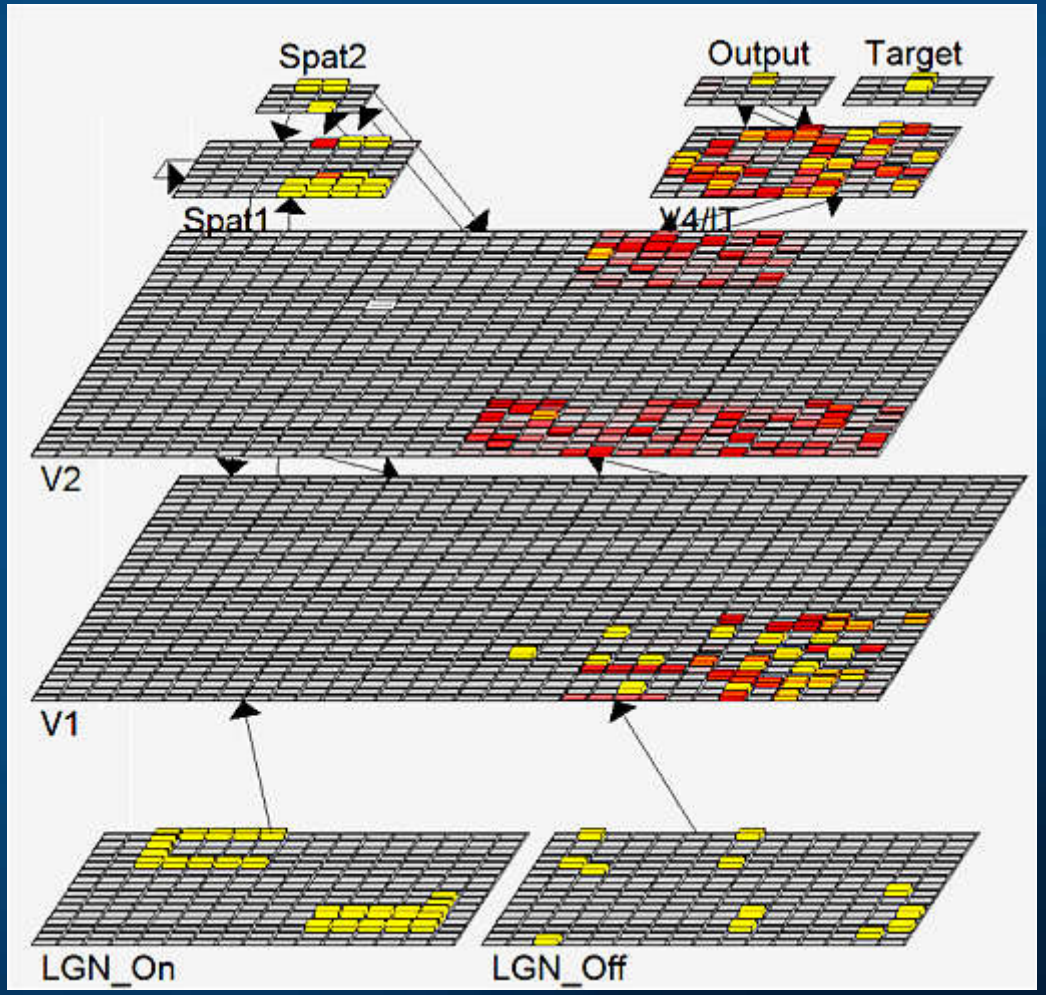
Spat1 ⇔ V2, Spat 2

Spat1 ⇔ V2, Spat 2

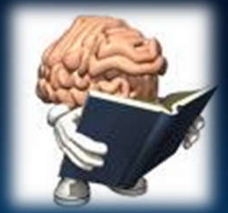
Spat2 ⇔ V2.

Spat1 has recurrent activations and inhibition, focusing on a single object.

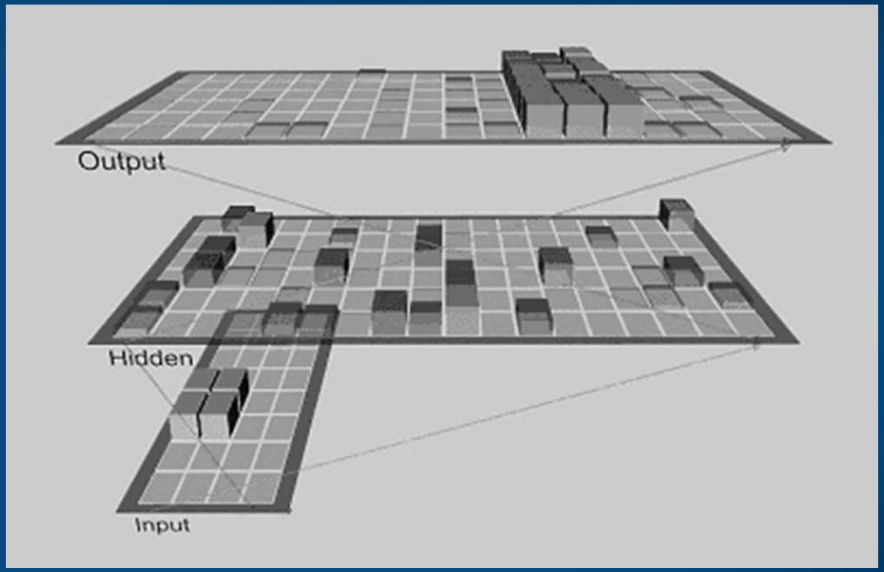
In normal situations neurons desynchronize and synchronize on the second object = attention shift.



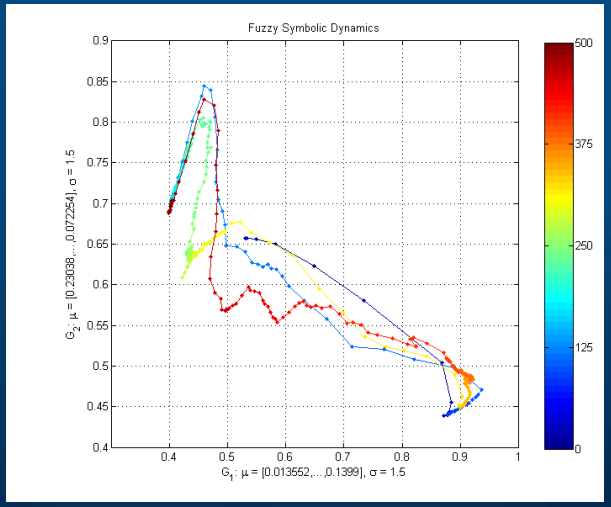
Model of movements

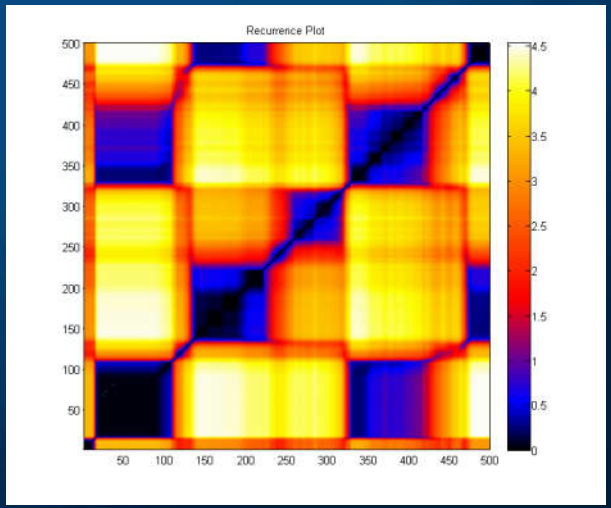


Model of cyclic movements was constructed using several simple patterns representing the movement of left and right arm, hand, leg, foot, reflected as a sequence of activations in the input layer with addition of the accommodation mechanism (i.e. neural fatigue). Output layer represents activations within the motor cortex (left arm).

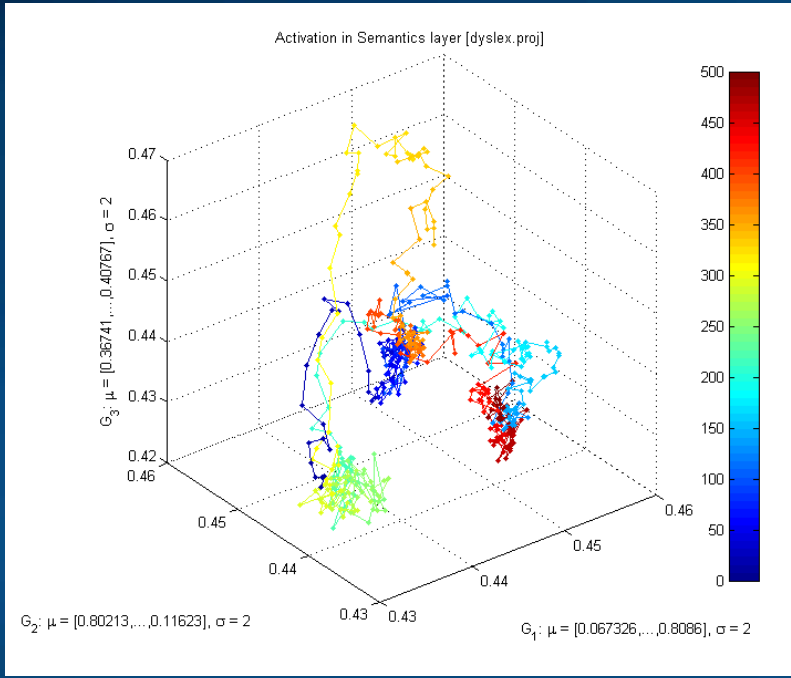


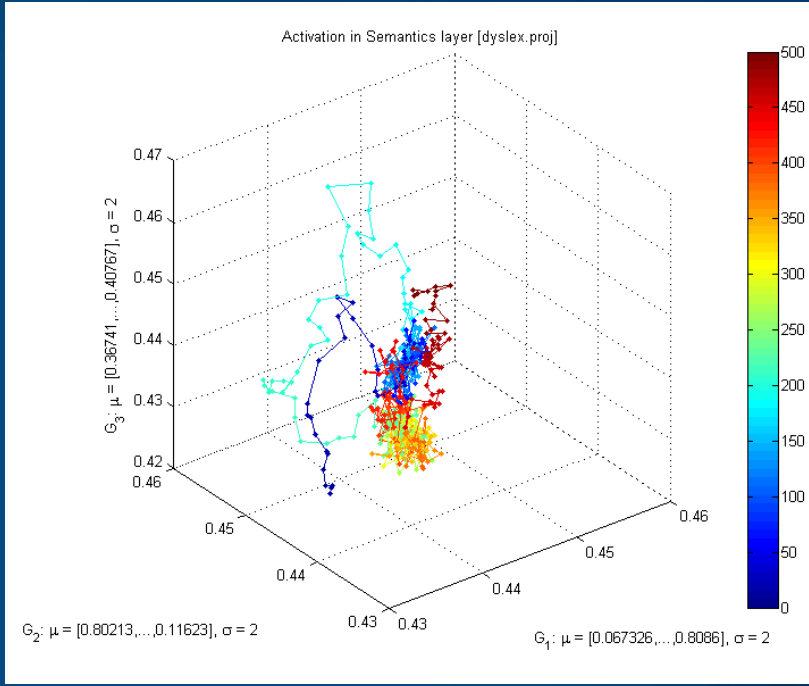
"Sliding attractors" are sometimes followed by irregular movements, ex. in speech, singing, gestures etc.





Normal-Autism



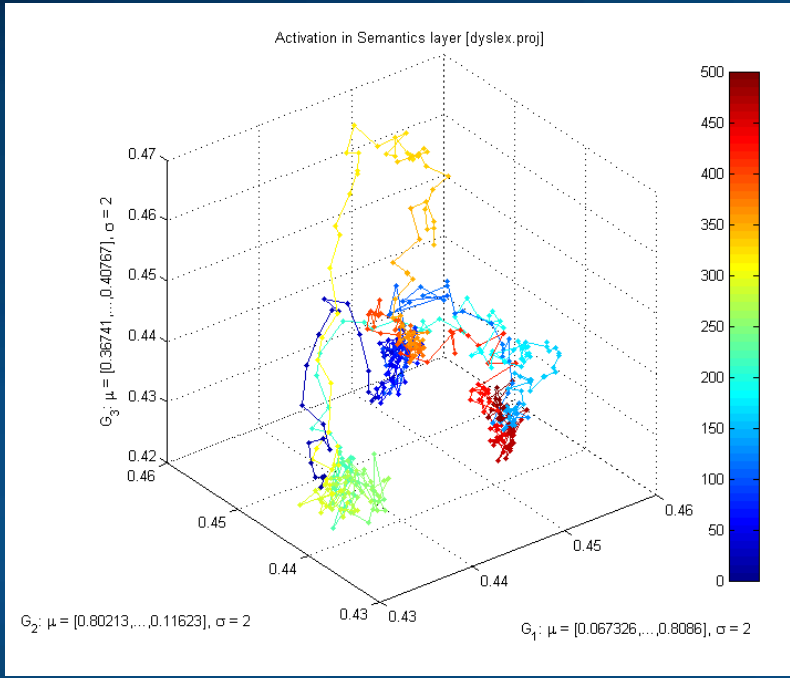


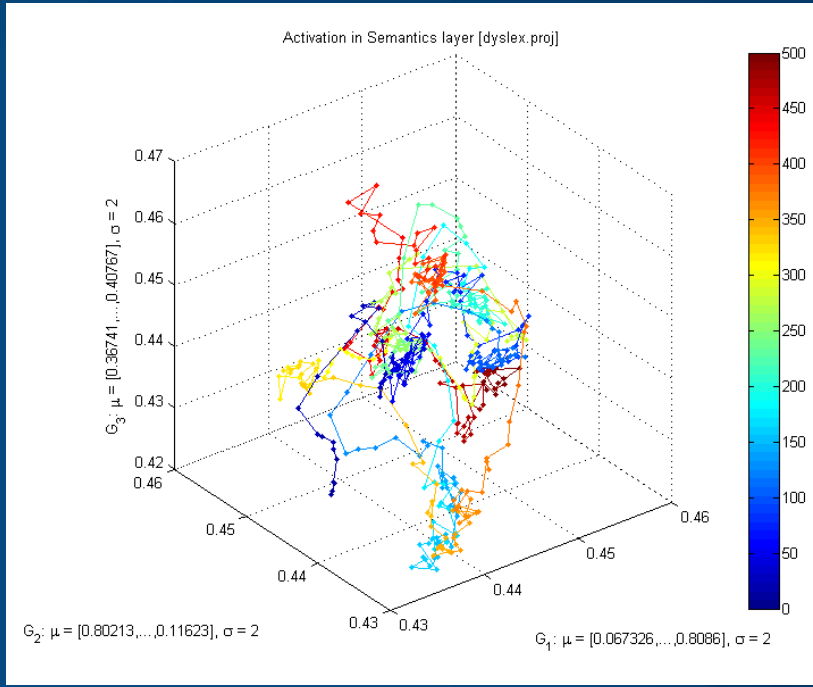
All plots for the flag word, different values of b_inc_dt parameter in the accommodation mechanism. b_inc_dt = 0.01 & b_inc_dt = 0.005

b_inc_dt = time constant for increases in intracellular calcium building up slowly as a function of activation, controls voltage-dependent leak channels.

http://kdobosz.wikidot.com/dyslexia-accommodation-parameters

Normal-ADHD





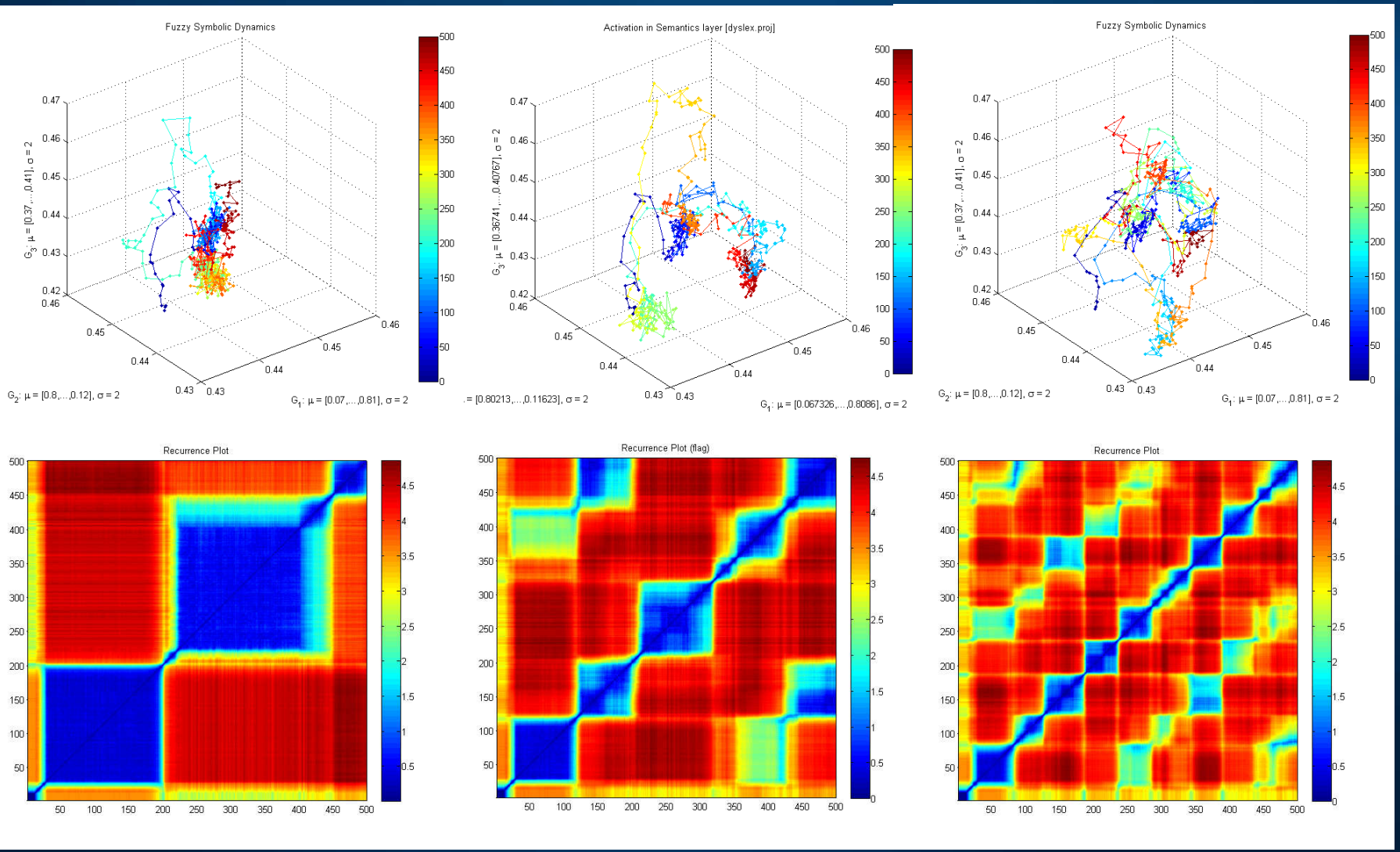
All plots for the flag word, different values of b_inc_dt parameter in the accommodation mechanism. b_inc_dt = 0.01 & b_inc_dt = 0.02

b_inc_dt = time constant for increases in intracellular calcium which builds up slowly as a function of activation.

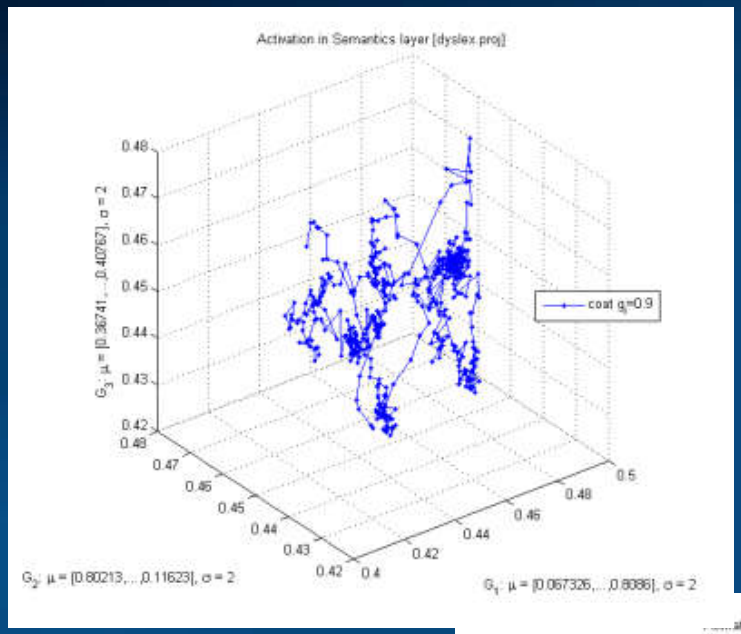
http://kdobosz.wikidot.com/dyslexia-accommodation-parameters

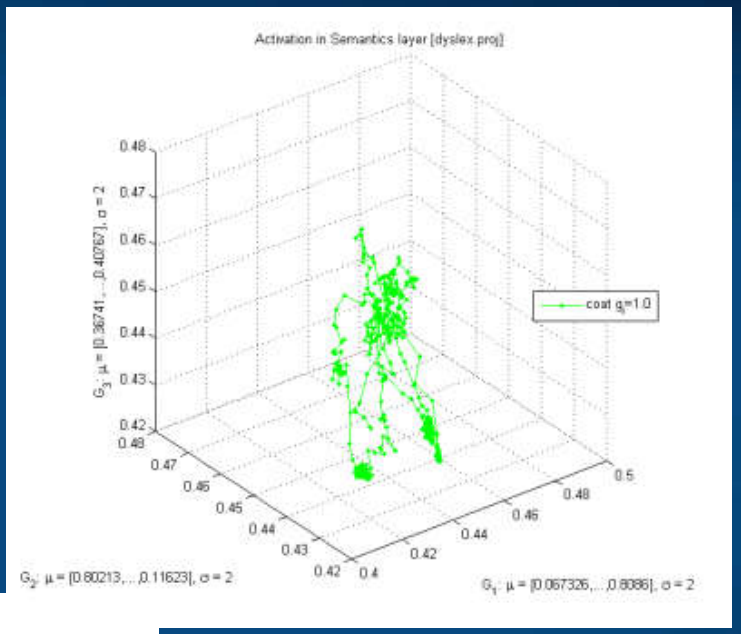
Autism-Normal-ADHD

b_inc_dt = 0.005 *b_inc_dt* = 0.01 *b_inc_dt* = 0.02

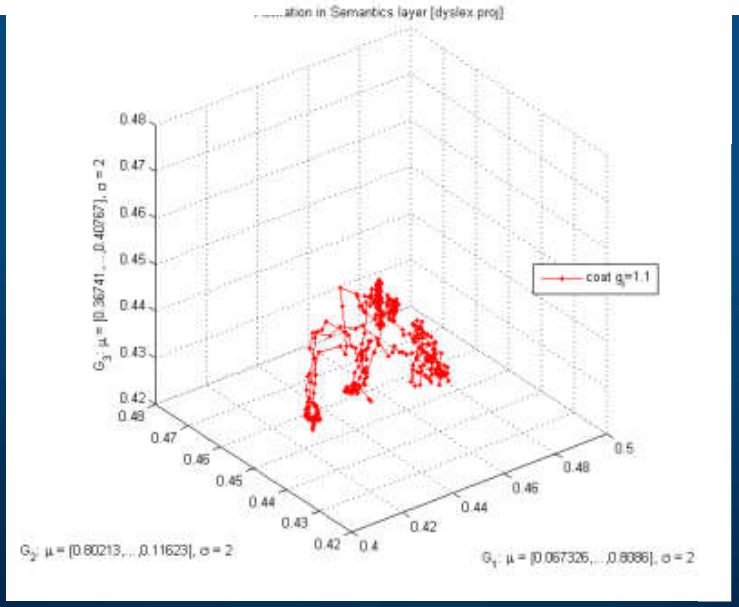


Inhibition



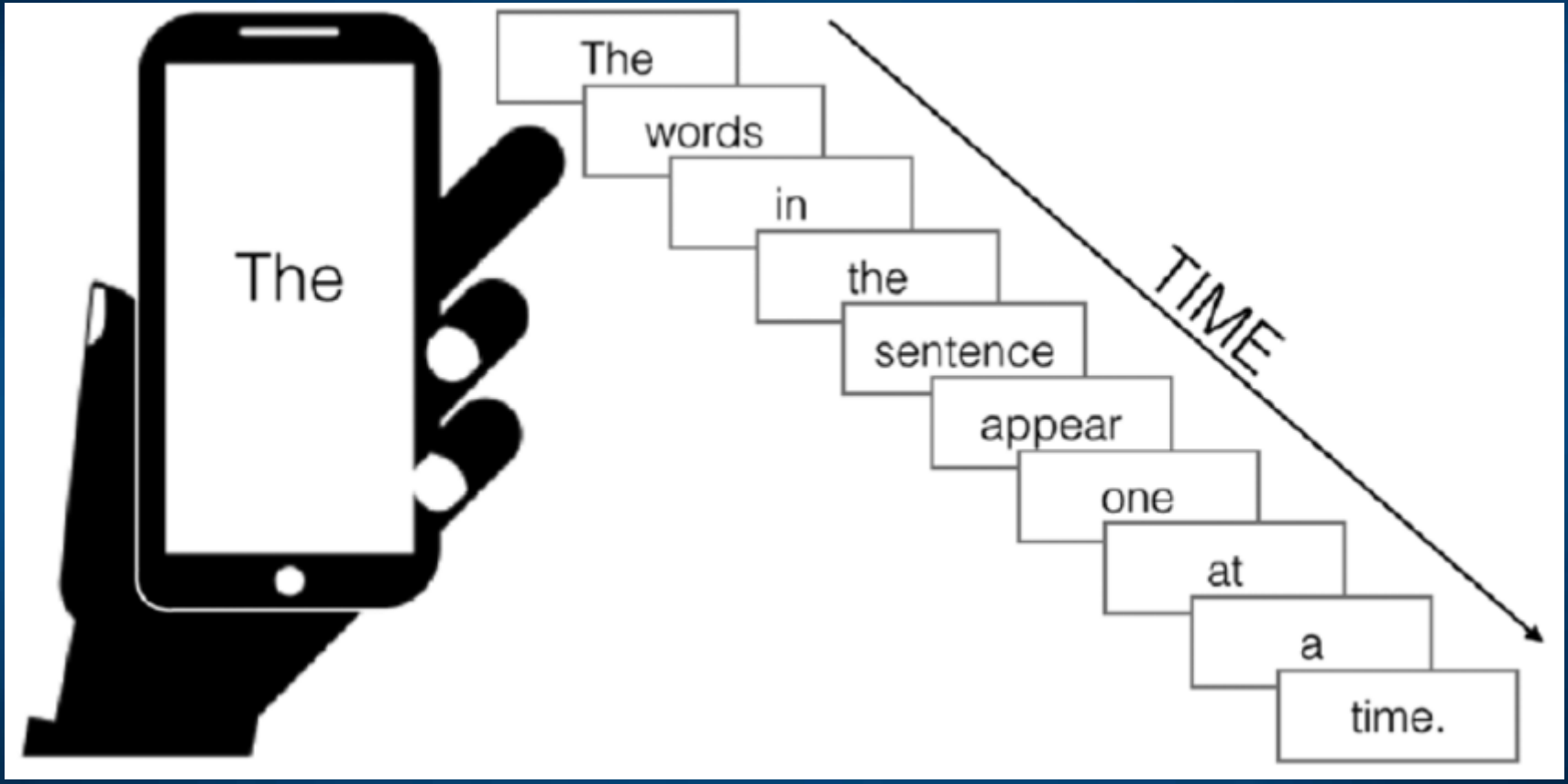


Increasing g_i from 0.9 to 1.1 reduces the attractor basin sizes and simplifies trajectories.



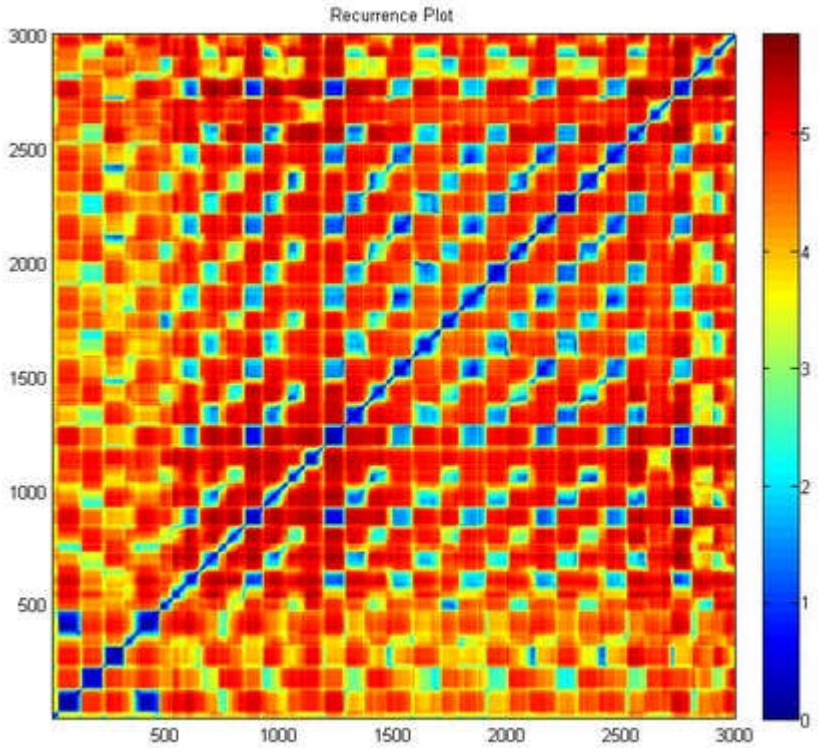
Strong inhibition, empty head …

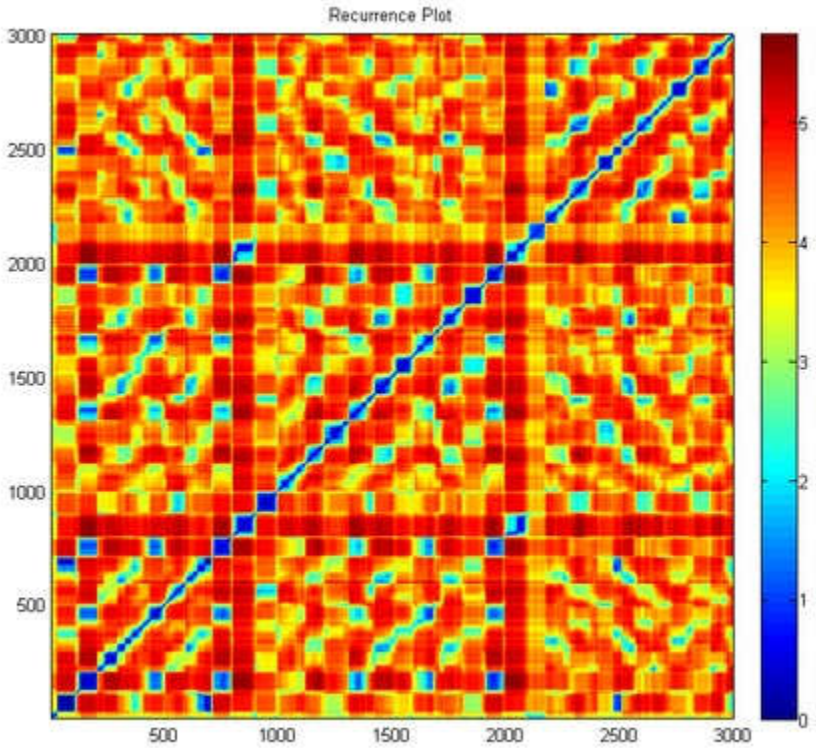
Rapid Serial Visual Presentation



Simulation: showing series of words, looking for attention/associations.
star => flea => tent => lock => tart => hind

RSVP simulations: normal



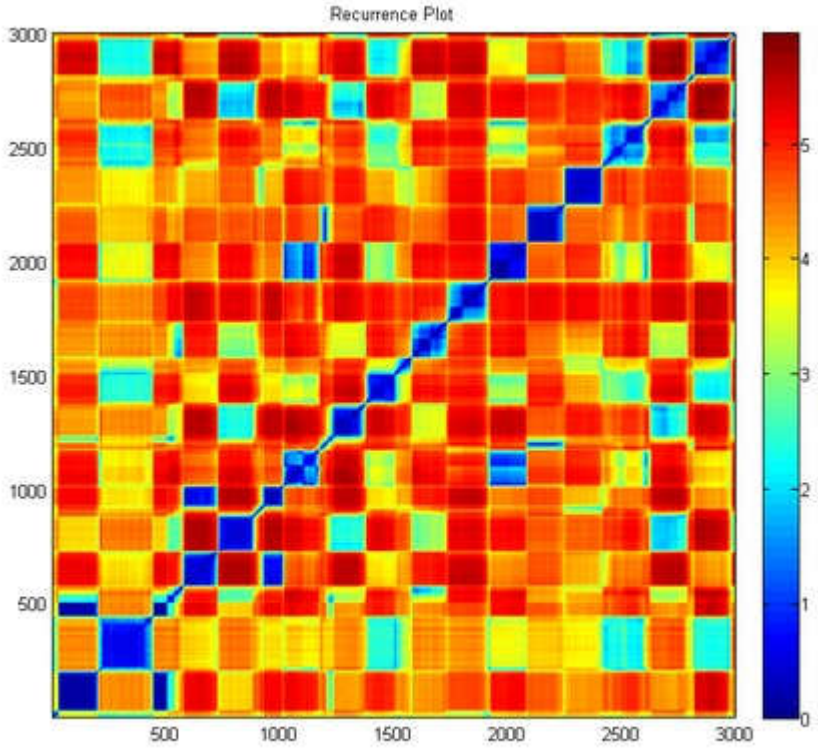


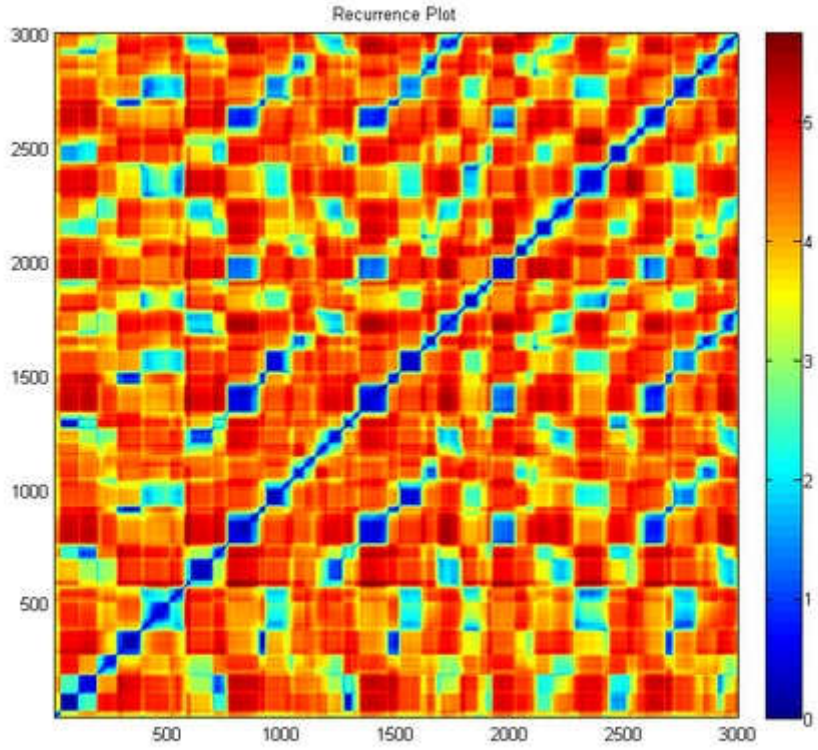
Typical case: accommodation

b_inc_dt = 0.01, normal presentation
500 it/word

b_inc_dt = 0.01, fast presentation
100 it/word

RSVP simulations:HFA



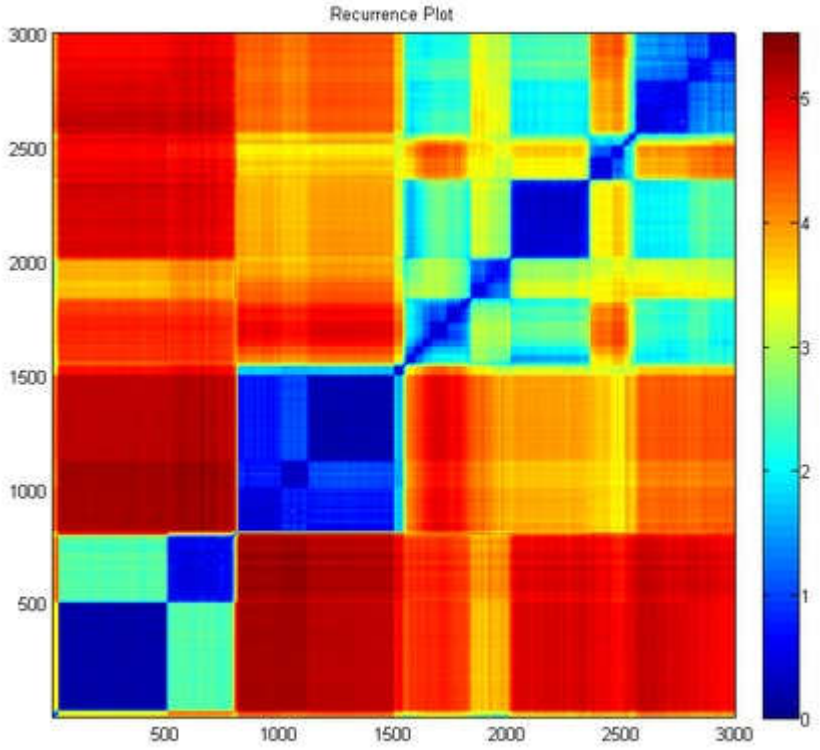


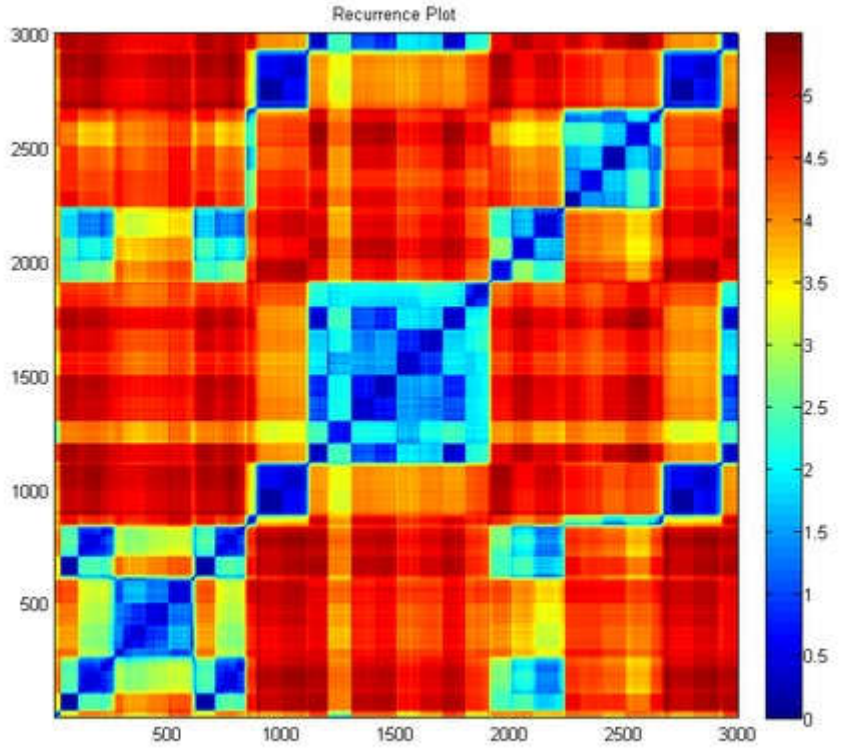
High functioning ASD case (HFA): accommodation

b_inc_dt = 0.005, normal presentation
500 it/word

b_inc_dt = 0.005, fast presentation
100 it/word

RSVP simulations: ASD





Severe ASD case: accommodation

b_inc_dt = 0.001, normal presentation
500 it/word

b_inc_dt = 0.001, fast presentation
100 it/word

Some speculations

Attention shifts may be impaired due to several factors:

1. Deep and narrow attractors that entrap dynamics – due to leak channels?

Explains overspecific memory in ASD, unusual attention to details, the inability to generalize visual and other stimuli but not olfactory.

2. Shallow and broad attractors:
   ADHD short attention span, need for psychostimulants to stablize ADHD.

3. Accommodation: voltage-dependent K^+ channels (~40 types) do not decrease depolarization in a normal way, attractors do not shrink.

This effect should also slow down attention shifts and reduce jumps to unrelated thoughts or topics relatively to average person – neural fatigue will temporarily switch them off preventing activation of attractors that code significantly overlapping concepts.

What behavioral changes are expected? How to tests it?

Slower processing – deep attractors

Hypothesis: deep attractors => longer trapping times => slower processing => lack of internal stimulations => underconnectivity.

Hedvall, Å., Fernell, E., Holm, A., Åsberg Johnels, J., Gillberg, C., & Billstedt, E. (2013). Autism, Processing Speed, and Adaptive Functioning in Preschool Children. The Scientific World Journal 2013, ID 158263

Haigh, S. M., Walsh, J. A., Mazefsky, C. A., Minshew, N. J., & Eack, S. M. (2018). Processing Speed is Impaired in Adults with Autism Spectrum Disorder, and Relates to Social Communication Abilities. *Journal of Autism and Developmental Disorders*. Epub ahead of print.

Good measure of brain processing speeds?
Wechsler Preschool and Primary Scale of Intelligence-III subtests “Coding and Symbol Search” comprise the processing speed quotients (PSQs).
Subtests on the MATRICS Consensus Cognitive Battery.

Experimental evidence: behavior

Kawakubo Y, et al. Electrophysiological abnormalities of spatial attention in adults with autism during the gap overlap task. Clinical Neurophysiology 118(7), 1464-1471, 2007.

- "These results demonstrate electrophysiological abnormalities of disengagement during visuospatial attention in adults with autism which cannot be attributed to their IQs."
- "We suggest that adults with autism have deficits in attentional disengagement and the physiological substrates underlying deficits in autism and mental retardation are different."

Landry R, Bryson SE, Impaired disengagement of attention in young children with autism. Journal of Child Psychology and Psychiatry 45(6), 1115 - 1122, 2004

- "Children with autism had marked difficulty in disengaging attention. Indeed, on 20% of trials they remained fixated on the first of two competing stimuli for the entire 8-second trial duration."

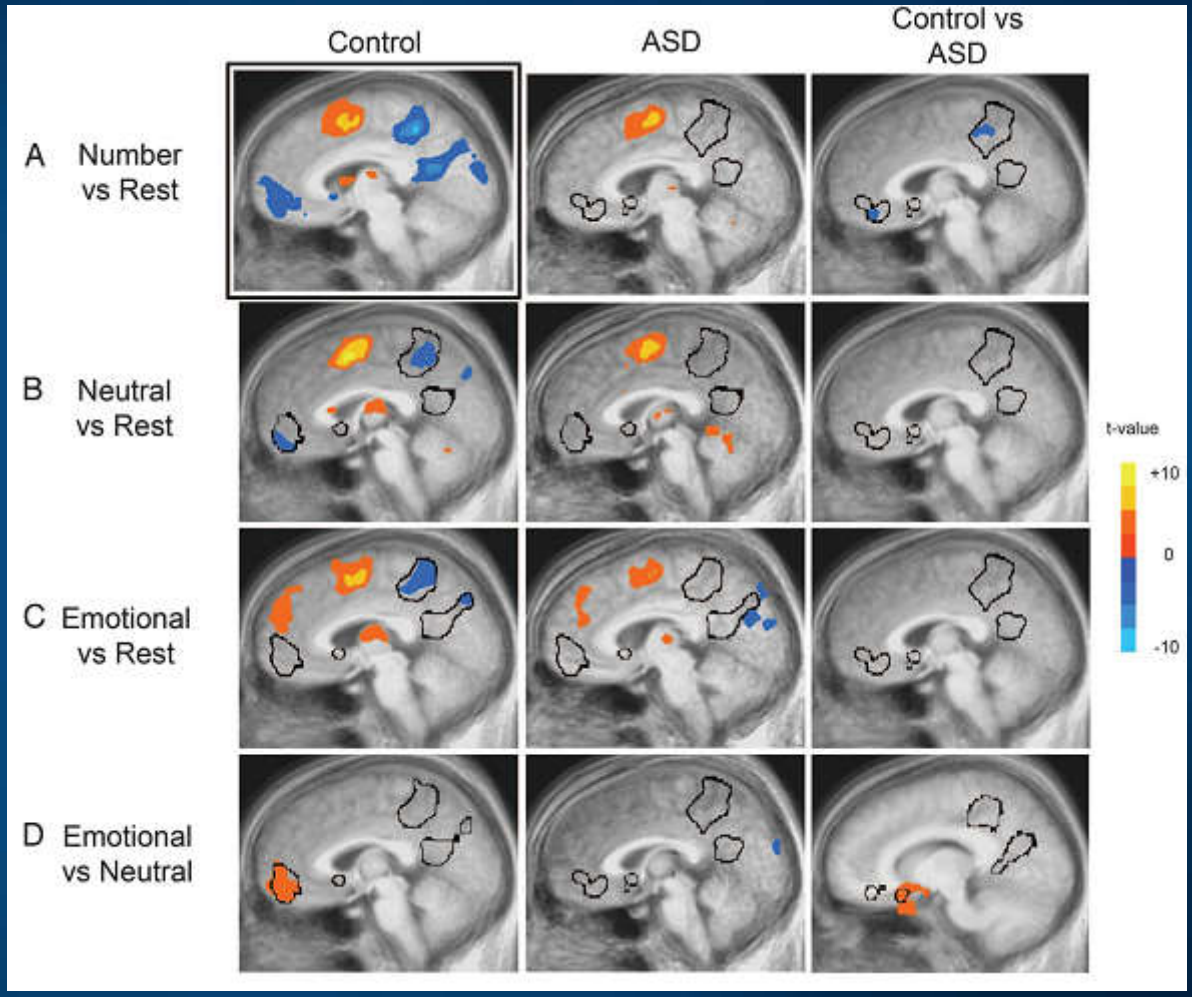
Several newer studies: Mayada Elsabbagh.

Experimental evidence: behavior

D.P. Kennedy, E. Redcay, and E. Courchesne,

Failing to deactivate: Resting functional abnormalities in autism. PNAS 103, 8275-8280, 2006.

Default network in autism group failed to deactivate brain regions, strong correlation between a clinical measure of social impairment and functional activity within the ventral MPF.



Mistaking symptoms for real problems:
We speculate that the lack of deactivation in the autism group is indicative of abnormal internally directed processes at rest.

Mistaking symptoms for causes

Various brain subsystems develop in an abnormal way:

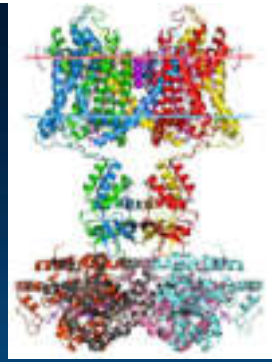
1. **Abnormal functional connectivity** between extra striate and temporal cortices during attribution of mental states, and executive tasks such as memory for or attention to social information (Castelli et al., 2002 ; Just et al., 2004, 2007; Kana et al., 2007a, b; Dichter et al., 2007; Kleinhans et al., 2008).

2. Underconnectivity: working memory, face processing (Just et al., 2007; Koshino et al., 2008; Bird et al., 2006), cortico-cortical connectivity (Barnea-Goraly et al., 2004; Herbert et al., 2004; Keller et al., 2007).

3. **Default mode** network: "Results revealed that while typically developing individuals showed enhanced recall skills for negative relative to positive and neutral pictures, individuals with ASD recalled the neutral pictures as well as the emotional ones. Findings of this study thus point to reduced influence of emotion on memory processes in ASD than in typically developing individuals, possibly owing to amygdala dysfunctions."

C. Deruelle et al., Negative emotion does not enhance recall skills in adults with autistic spectrum disorders. Autism Research 1(2), 91–96, 2008

Experimental evidence: molecular

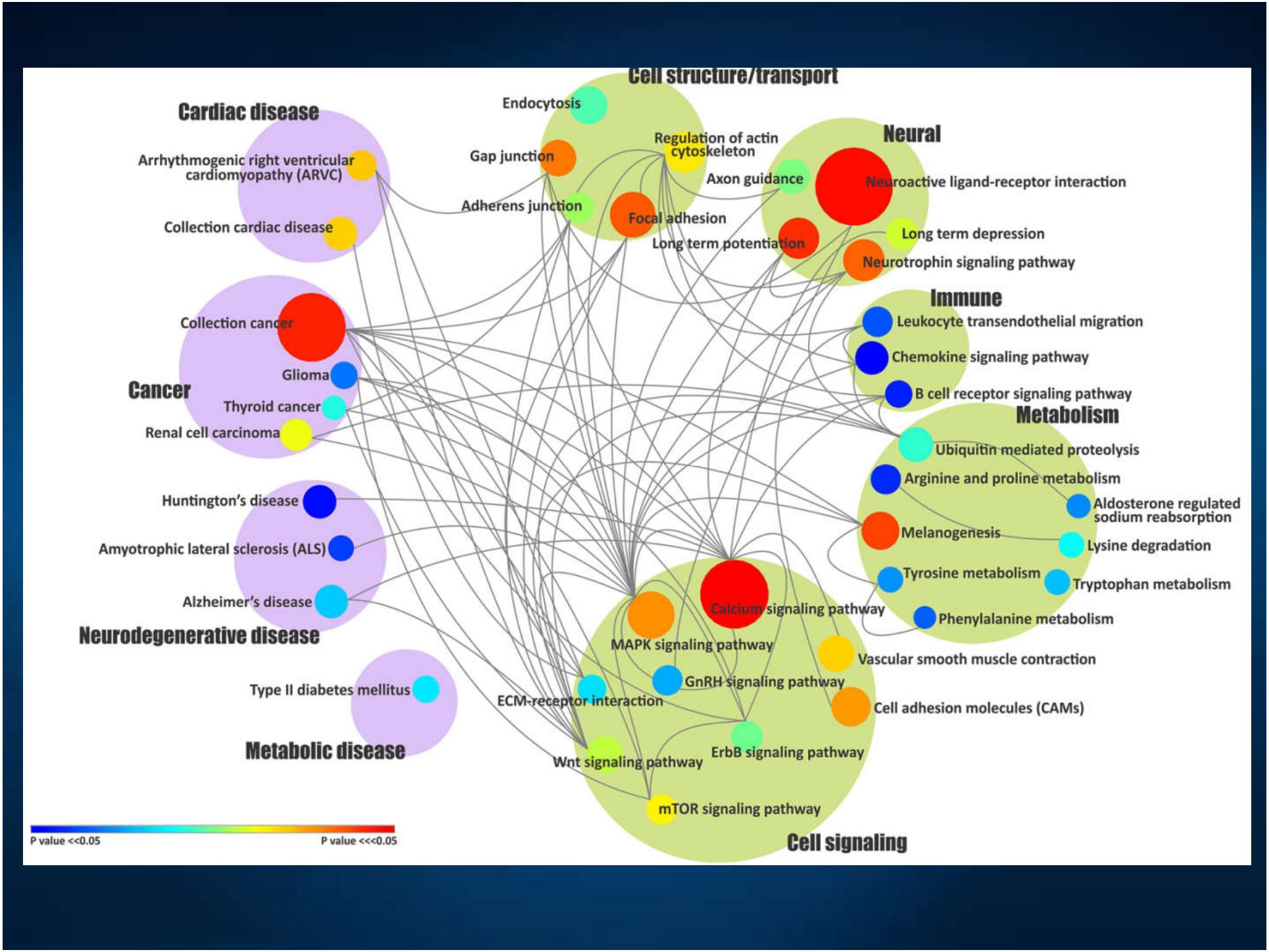


What type of problems with neurons create these types of effects?

- Neural self-regulation mechanisms lead to fatigue or accommodation of neurons through leaky K^+ channels opened by high Ca^{++} concentration, or longer acting GABA-B inhibitory synaptic channel.
- This leads to inhibition of neurons that require stronger activation to fire.
- Neurons accommodate or fatigue and become less and less active for the same amount of excitatory input.

Dysregulated calcium signaling, mainly through voltage-gated calcium channels (VGCC) is the central molecular event that leads to pathologies of autism.
http://www.autismcalciumchannelopathy.com/
Calcium homeostasis in critical stages of development may be perturbed by genetic polymorphism related to immune function and inflammatory reactions and environmental influences (perinatal hypoxia, infectious agents, toxins).

Genetic mutations => proteins building incorrect potassium channels (CASPR2 gene) and sodium channels (SCN2A gene).

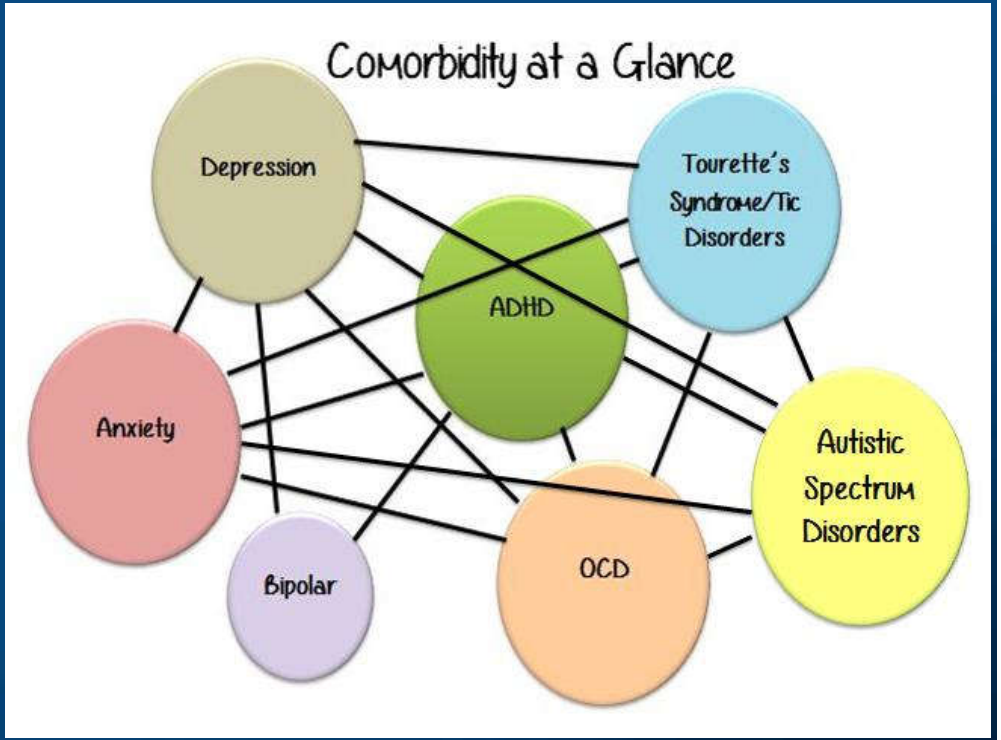

Cardiac disease
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Collection cardiac disease
Cell structure/transport
Endocytosis
Gap junction
Regulation of actin cytoskeleton
Adherens junction
Focal adhesion
Neural
Axon guidance
Neuroactive ligand-receptor interaction
Long term potentiation
Long term depression
Neurotrophin signaling pathway
Immune
Leukocyte transendothelial migration
Chemokine signaling pathway
B cell receptor signaling pathway
Collection cancer
Glioma
Cancer
Thyroid cancer
Renal cell carcinoma
Metabolism
Ubiquitin mediated proteolysis
Arginine and proline metabolism
Aldosterone regulated sodium reabsorption
Melanogenesis
Lysine degradation
Tyrosine metabolism
Tryptophan metabolism
Phenylalanine metabolism
Huntington's disease
Amyotrophic lateral sclerosis (ALS)
Alzheimer's disease
Neurodegenerative disease
Calcium signaling pathway
MAPK signaling pathway
Vascular smooth muscle contraction
GnRH signaling pathway
ECM-receptor interaction
Cell adhesion molecules (CAMs)
ErbB signaling pathway
Wnt signaling pathway
mTOR signaling pathway
Type II diabetes mellitus
Metabolic disease
Cell signaling
P value <<0.05
P value <<<0.05

Comorbidity

Many diseases are observed together with ASD symptoms.

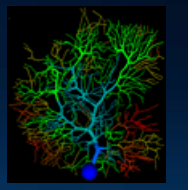
Most frequent are:

- Hearing problems,
- Epilepsy, migraines,
- Various mental problems,
- Metabolic and digestion,
- Various allergies, skin, food, astma
- ADHD?



Dysfunction of neurons but also
of other types of cells due to the
low-level molecular mechanisms that influence metabolic and neural processes.

Questions/Ideas

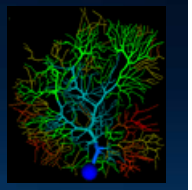


Neurodynamics is a new useful language to speak about mental processes.

There are many parameters characterizing biophysical properties of neurons and their connections within different layers that control behavior.

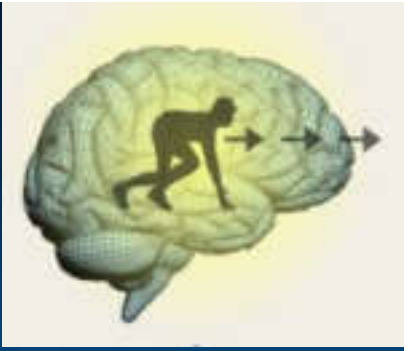
- How does depth/size of basins of attractors depend on these parameters?
- How to measure and/or visualize attractors?
- How do attractors depend on the dynamics of neuron accommodation? Noise? Inhibition strength, local excitations, long-distance synchronization?
- Stability of more detailed neural models, real effects or artifacts?
- How will symptoms differ depending on specific brain areas? For example, *mu* suppression may be due to deep attractors …
- What are precise relations to ion channels and proteins that build them?
- How can they be changed by pharmacological interventions?

More questions/ideas



- How learning procedures may influence formation of basins of attractors? For example, learning to read may depend on the variability of fonts, handwriting may be much more difficult etc.
- Slow broadening of attractor basins?
- Spontaneous thoughts, local energy with low neural accommodation?
- Can one draw useful suggestions how to compensate for such deficits?
- Spatial attention shifts in Posner experiments – resonances depending on the timing, masking effects, flickering with different frequencies?
- Precise diagnostics, what type of problems at genetic/molecular level?
- Compensation effects: what changes in the network will lead to faster attention shifts?
- Will it help in diagnostics/therapy? Neurofeedback?
  We need to finish computational simulations and then do real test of some predictions.

Neurons and dynamics



Trajectories show spontaneous shifts of attention.

- Attention shifts may be impaired due to the deep and narrow attractor basins that entrap dynamics – dysfunction of leak channels (~15 types)?

In memory models overspecific memories are created (as in ASD), unusual attention to details, the inability to generalize visual and other stimuli.

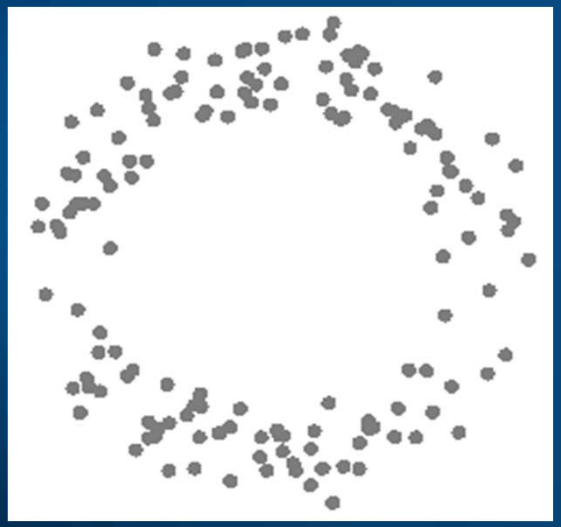
- Accommodation: voltage-dependent K^+ channels (~40 types) do not decrease depolarization in a normal way, attractors do not shrink.

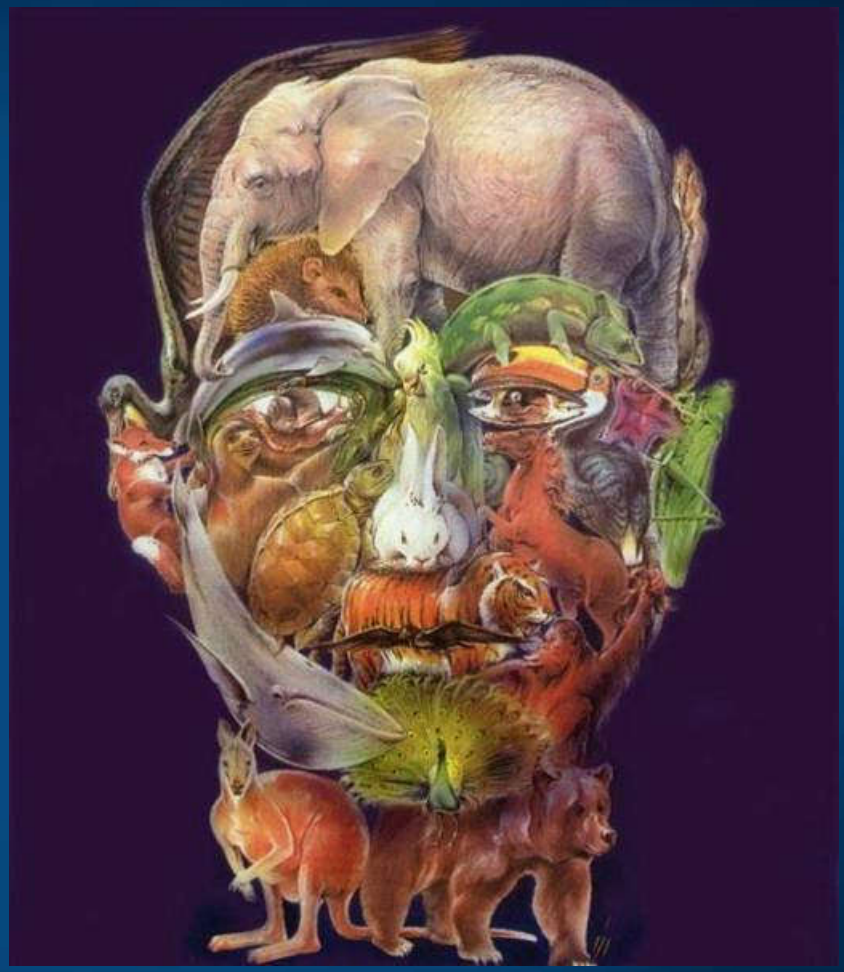
This should slow down attention shifts and reduce jumps to unrelated thoughts or topics (in comparison to average person).
Neural fatigue temporarily turns some attractors off, making all attractors that code significantly overlapping concepts inaccessible.

This is truly dynamic picture: attractor landscape changes in time!

What behavioral changes are expected depending on connectivity, inhibition, accommodation dynamics, leak currents, etc?

Thank for
synchronization
of your neurons





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