

Critical review of current Autism Spectrum Disorders theories

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Psychological, Genetic and Neurological Aspects of ASD Diagnosis, Gdańsk 19-20.10.2018,

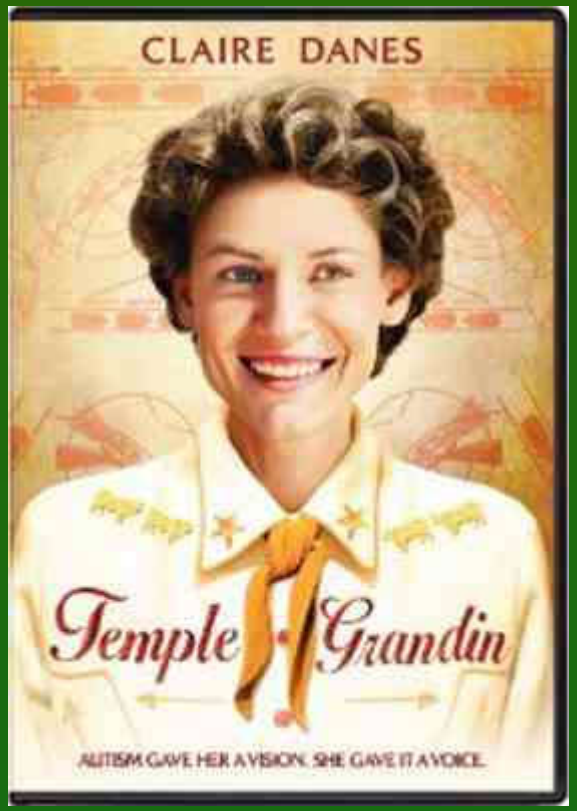
Plan:

- Can we understand autism spectrum disorder? What diagnostic and therapeutic consequences follow from various hypothesis?

- Theories: symptoms or causes?
- Genetics and molecular level.
- Brain structures and their connections.
- Diagnostic breakthroughs?
- Insights from computational models.
- Informed guesses … speculations.

Anthropologist from Mars

Temple Grandin, "The Woman Who Thinks Like a Cow"(BBC special)
http://templegrandin.com/



A bit of ASD history

ASD: Autism Spectrum Disorder, includes many forms of autism.

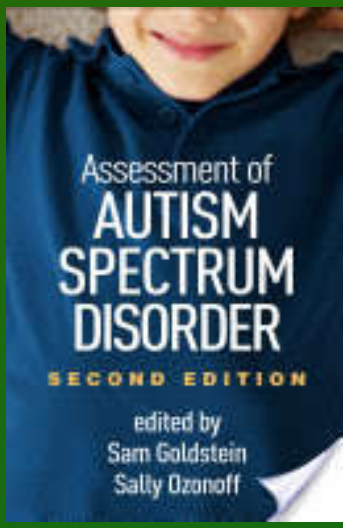
Described for the first time in 1943 by Leo Kanner:

- “extreme aloneness from the beginning of life and anxiously obsessive desire for the preservation of sameness.”
- “… these children have come into the world with innate inability to form the usual, biologically provided affective contact with people … ”.

Common deficit: lack of the theory of mind.

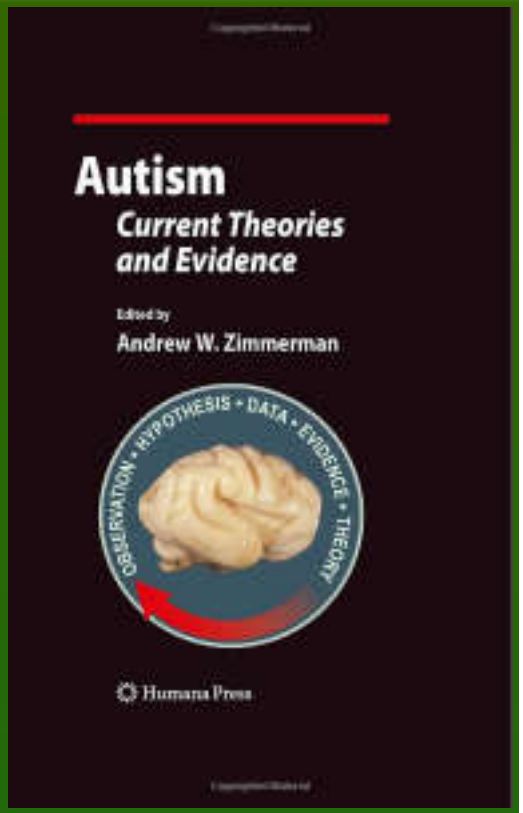
Initial theories:

- bad parents, refrigerator mothers ...
- a behavioral syndrome … a developmental syndrome ...



Distinguishing specific subtypes of autism is difficult: hence the name **Autism Spectrum Disorder**.
Conclusion: multiple disease forms, multiple etiologies, including metabolic and immune system deregulation, genetic mutations, and as a result abnormal brain development.

Theories & more theories



Overview of ASD theories:

Andrew W. Zimmerman (Ed.) Autism; current theories and evidence. Humana Press 2008.
„… as in many areas of neuroscience, we are ‘‘data rich and theory poor’’.

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).

Several others, ex: Grossberg ART model. All are true but some more then the others. Symptoms should not be taken as causes and real mechanisms.

Functional connectivity theory

Model developed over 20 years (Nancy J. Minshew): autism as widespread disorder of association cortex, development of connectivity, only secondarily as a behavioral disorder. Fine, but still quite general.

Abnormalities in genetic code for brain development

↓

Abnormal mechanisms of brain development

↓

Structural and functional abnormalities of brain

↓

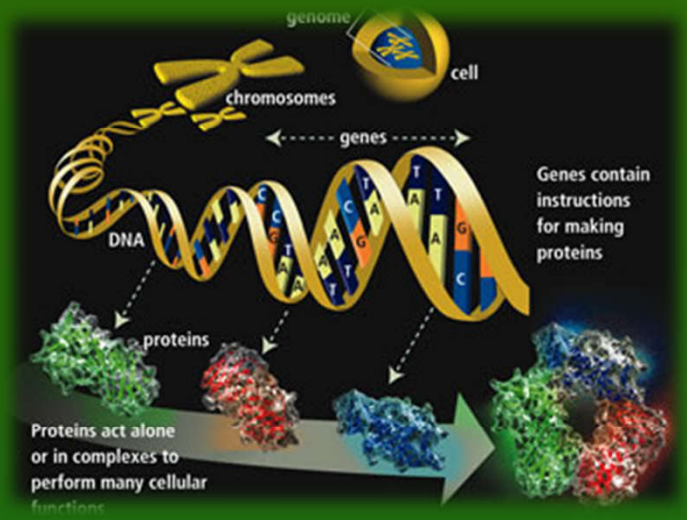
Cognitive and neurologic abnormalities

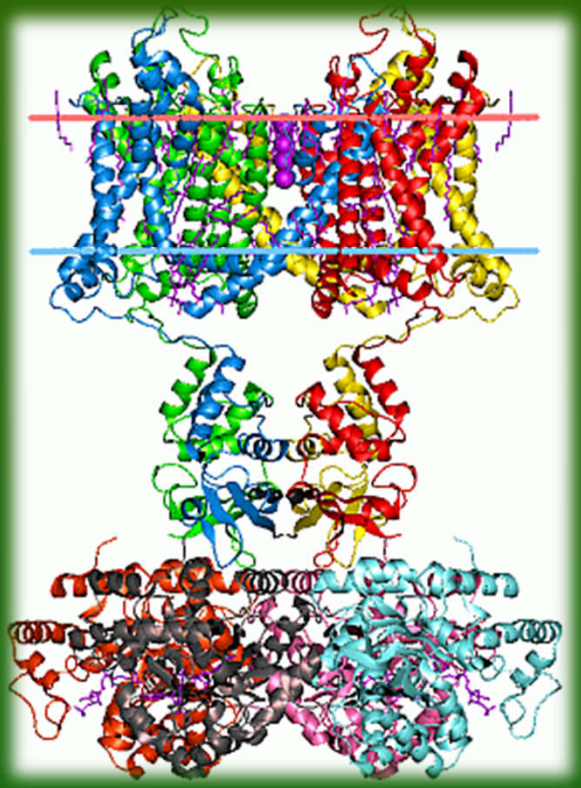
↓

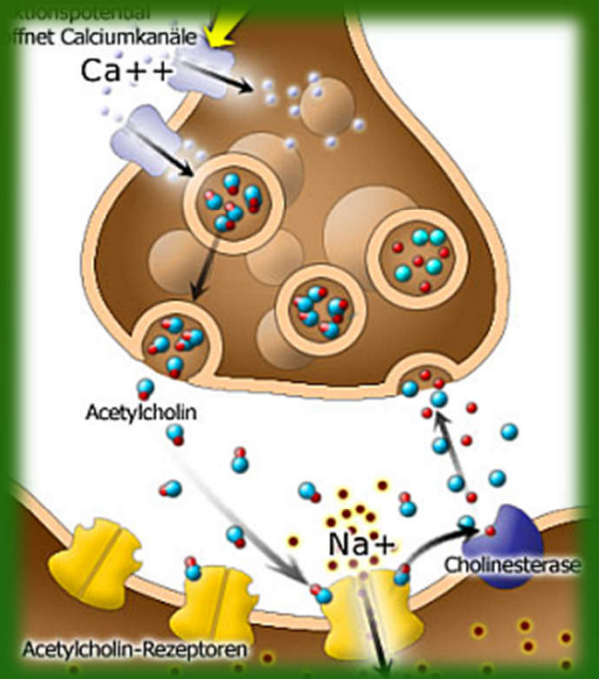
Behavioral syndrome-end result of atypical development?

Goal: understand the pathophysiology from gene to behavior, eventually the influence of etiologies on this sequence, ultimately support the development of interventions at multiple levels of the pathophysiologic sequence.

From Genes to Neurons

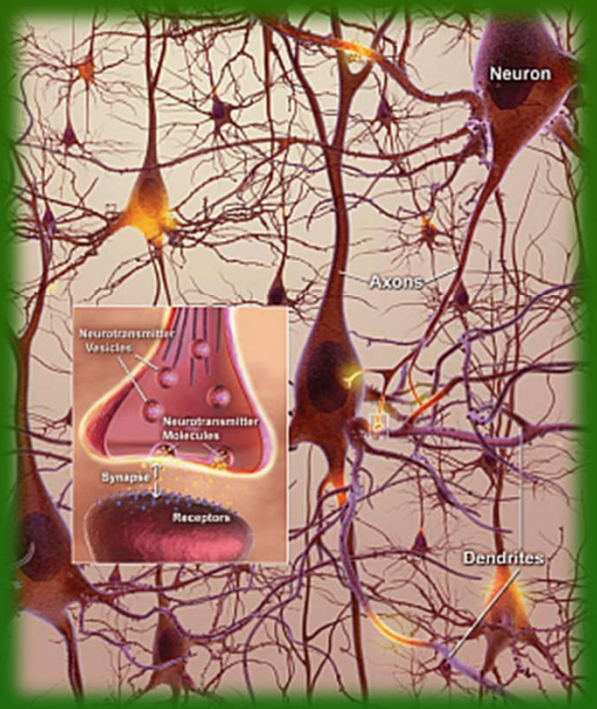


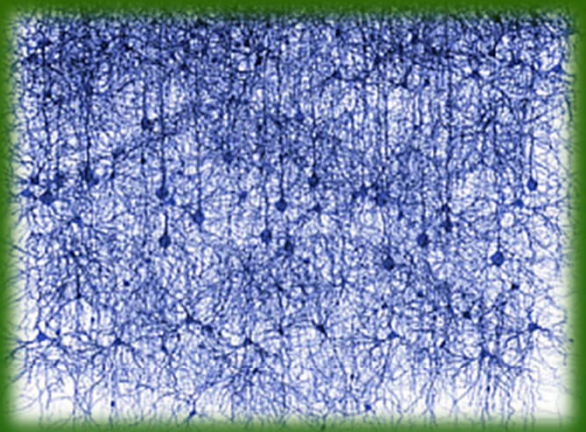


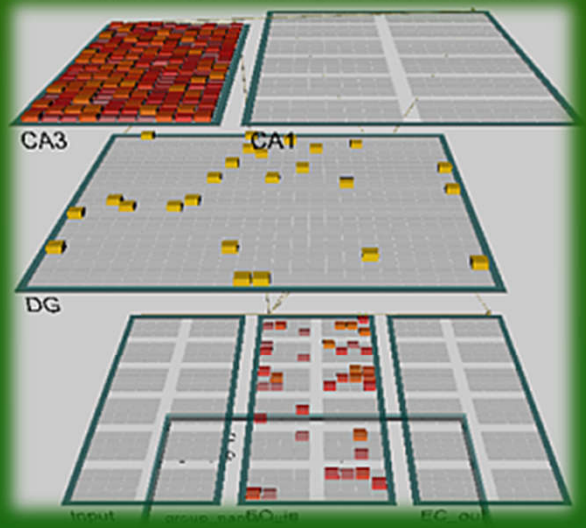


Genes => Proteins => receptors, ion channels, synapses
=> neuron properties, networks, neurodynamics
=> cognitive phenotypes, abnormal behavior, syndromes.

From Neurons to Behavior

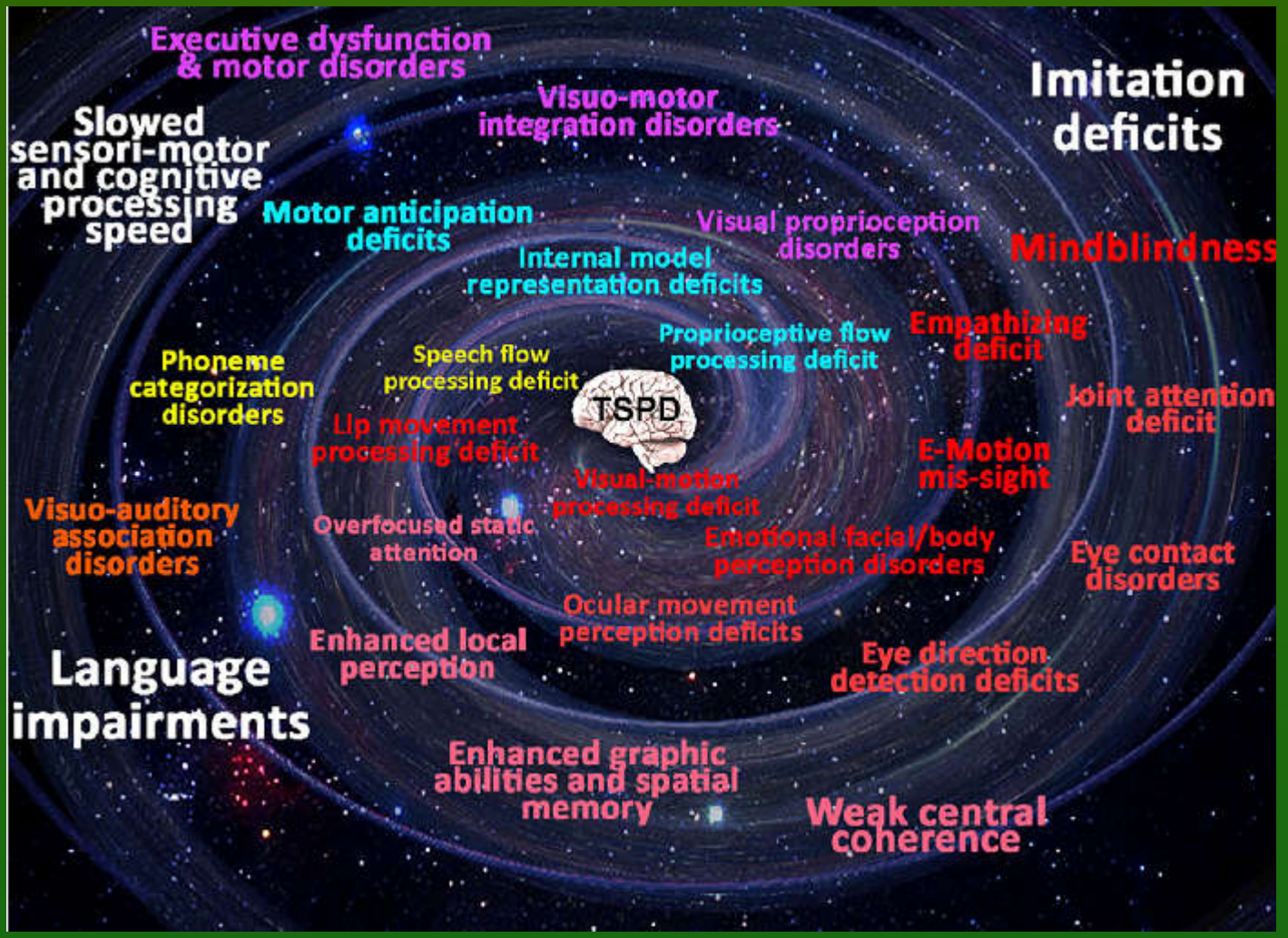






Genes => Proteins => receptors, ion channels, synapses
=> neuron properties, networks
=> neurodynamics => cognitive phenotypes, abnormal behavior!

Temporo-spatial processing disorders



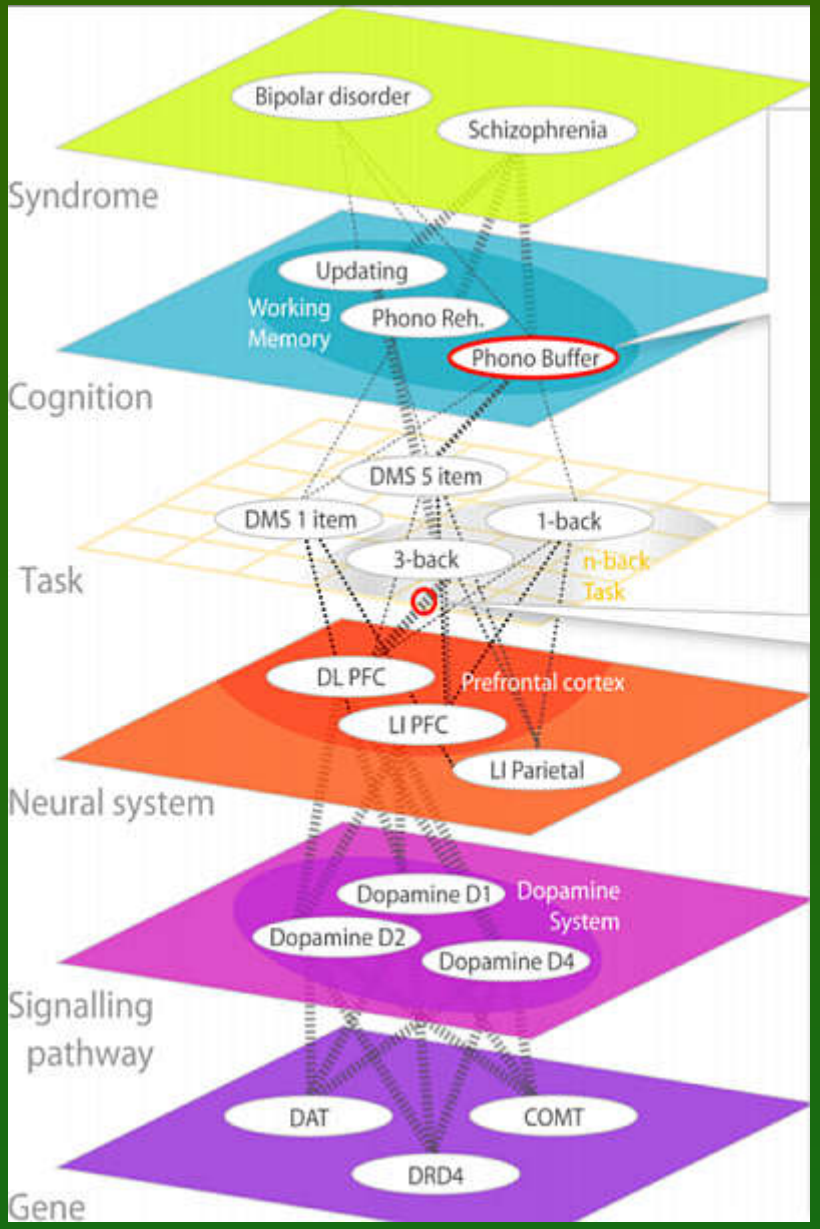
B. Gepner, F. Feron, Autism: A world changing too fast for a mis-wired brain? Neuroscience and Biobehavioral Reviews (2009).

Neuropsychiatric Phenomics Levels

According to
The Consortium for Neuropsychiatric Phenomics (CNP)
http://www.phenomics.ucla.edu

From genes to molecules to neurons and their systems to tasks, cognitive subsystems and syndromes.

Neurons and networks are right in the middle of this hierarchy.



NIMH RDoC Matrix for deregulation of large brain systems.

Instead of classification of mental disease by symptoms use **Research Domain Criteria** (RDoC) based on **multi-level neuropsychiatric phenomics**.

1. **Negative Valence Systems**, primarily responsible for responses to aversive situations or context, such as fear, anxiety, and loss.
2. **Positive Valence Systems** are primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning.
3. **Cognitive Systems** are responsible for various cognitive processes.
4. **Social Processes Systems** mediate responses in interpersonal settings of various types, including perception and interpretation of others' actions.
5. **Arousal/Regulatory Systems** are responsible for generating activation of neural systems as appropriate for various contexts, providing appropriate homeostatic regulation of such systems as energy balance and sleep.

RDoC Matrix for „cognitive domain”

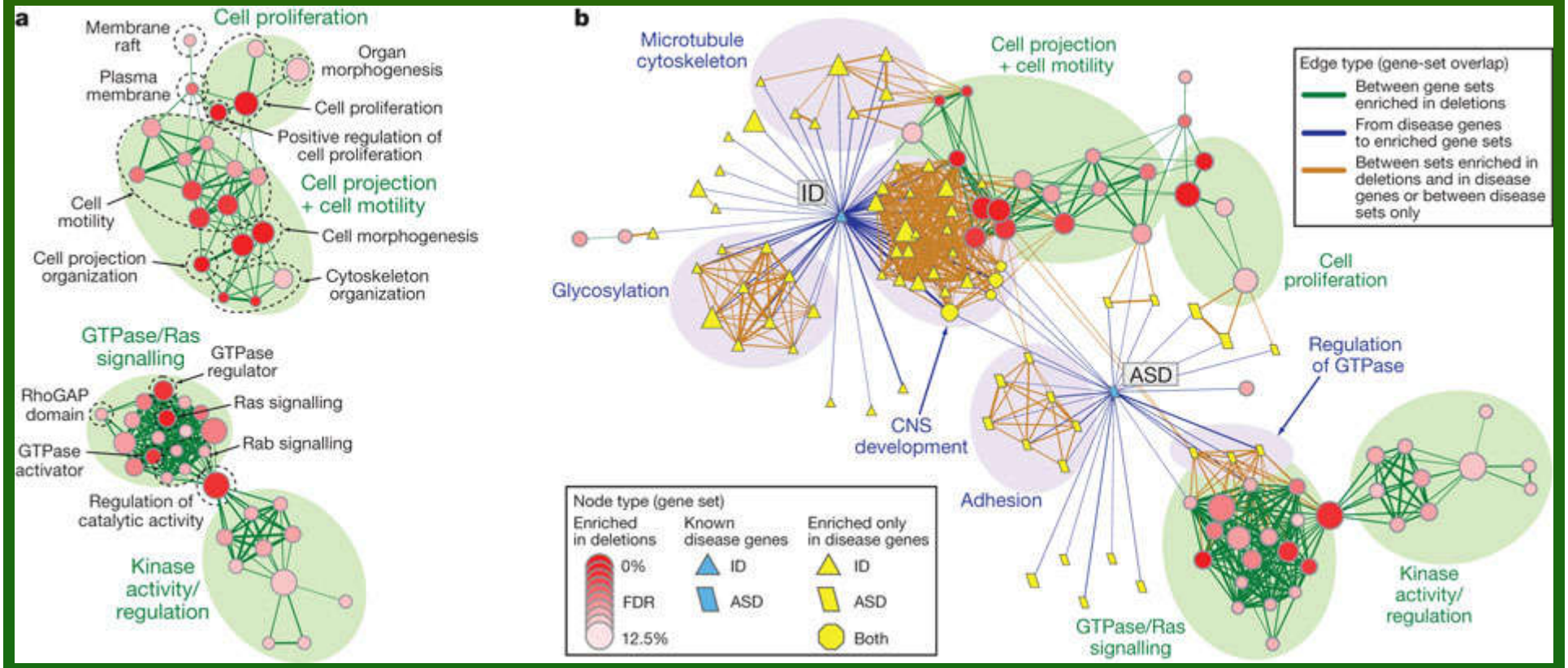
Construct/Subconstruct		Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
Attention		Elements	Elements	Elements	Elements	Elements	Elements		Elements
Perception	Visual Perception	Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Auditory Perception	Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Olfactory/Somatosensory/Multimodal/Perception								Elements
Declarative Memory		Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
Language		Elements			Elements	Elements	Elements	Elements	Elements
Cognitive Control	Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 1 of 2 ⇒ Goal Selection				Elements			Elements	Elements
	Goal Selection; Updating, Representation, and Maintenance ⇒ Focus 2 of 2 ⇒ Updating, Representation, and Maintenance	Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Response Selection; Inhibition/Suppression ⇒ Focus 1 of 2 ⇒ Response Selection	Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Response Selection; Inhibition/Suppression ⇒ Focus 2 of 2 ⇒ Inhibition/Suppression	Elements	Elements	Elements	Elements	Elements	Elements	Elements	Elements
	Performance Monitoring	Elements	Elements		Elements	Elements	Elements	Elements	Elements
Working Memory	Active Maintenance	Elements	Elements	Elements	Elements	Elements			Elements
	Flexible Updating	Elements	Elements	Elements	Elements	Elements			Elements
	Limited Capacity	Elements	Elements		Elements	Elements			Elements
	Interference Control	Elements	Elements	Elements	Elements	Elements			Elements

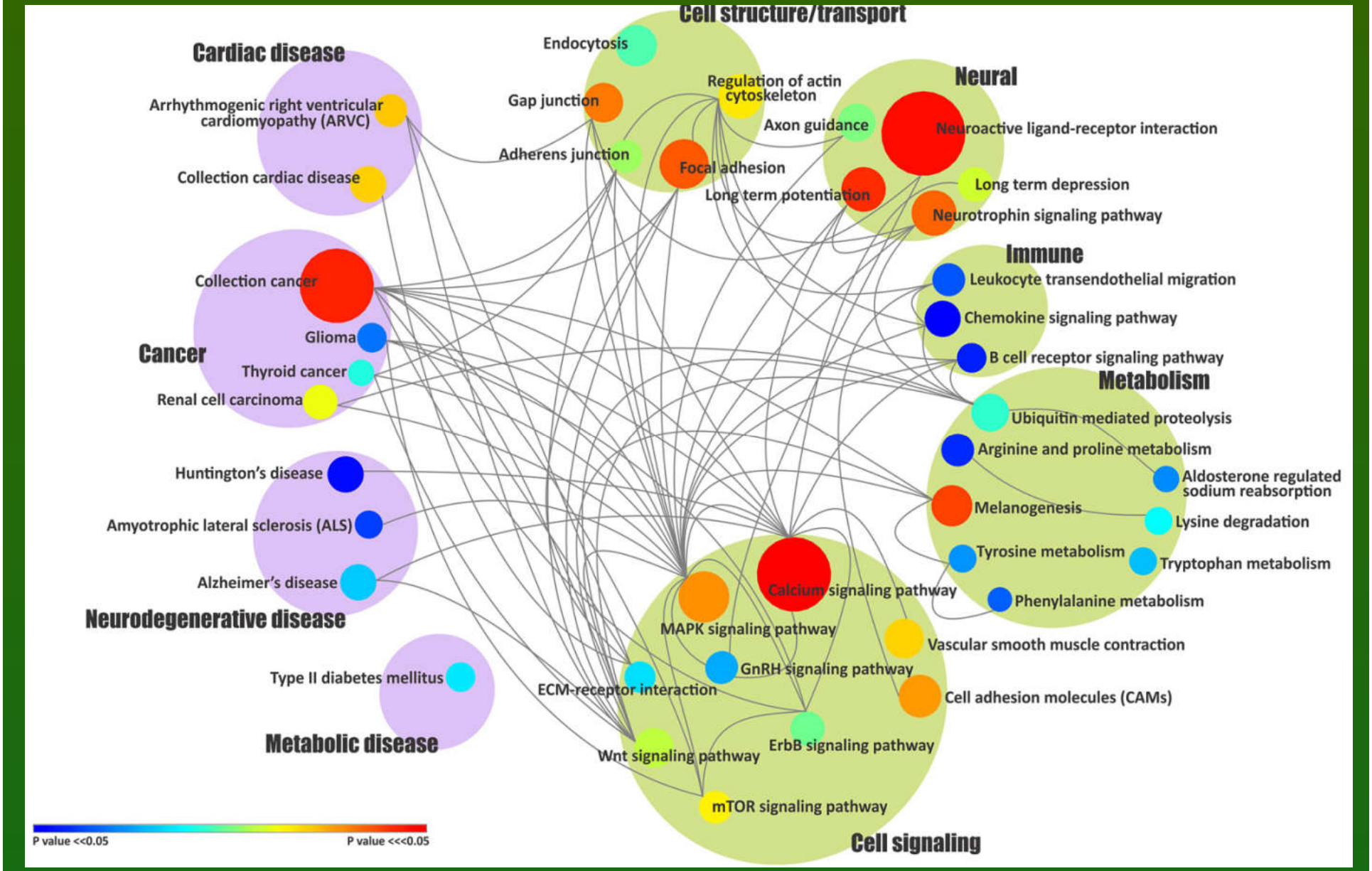
Genetics and molecular level

Genes & functions

Pinto, D. + 180 coauthors ... (2010). Functional impact of global rare copy number variation in autism spectrum disorders. Nature 466(7304):368-72

SFARI Human Gene Module database in 1/2018 listed 991 ASD genes.



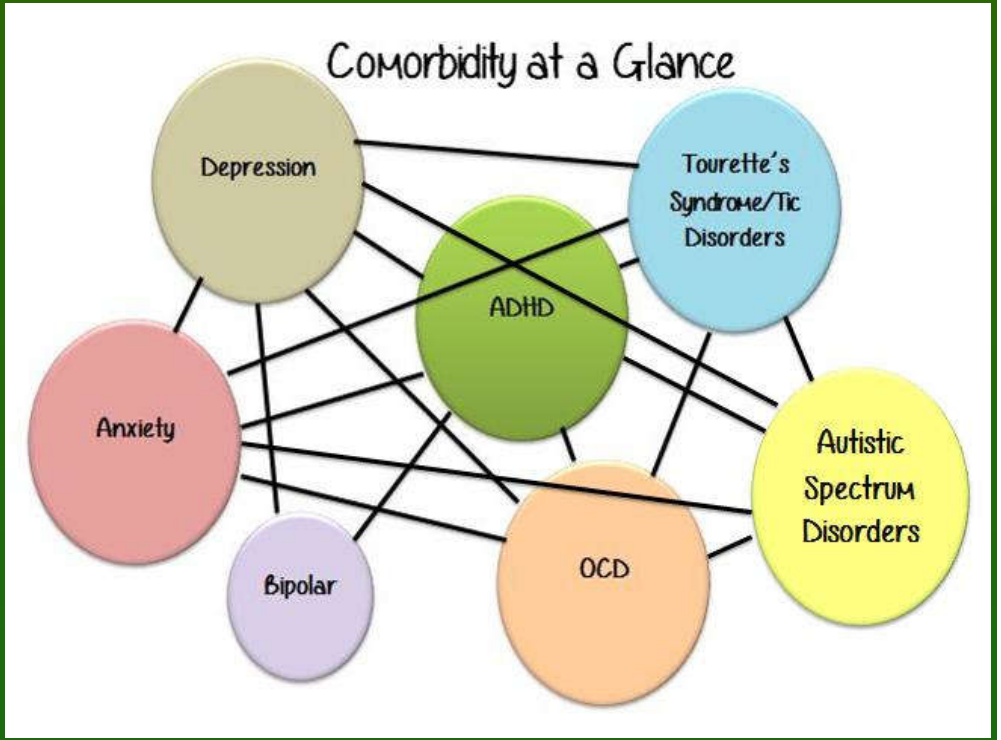

Cell structure/transport
Endocytosis
Regulation of actin cytoskeleton
Gap junction
Adherens junction
Focal adhesion
Cardiac disease
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Collection cardiac disease
Neural
Axon guidance
Neuroactive ligand-receptor interaction
Long term potentiation
Long 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.

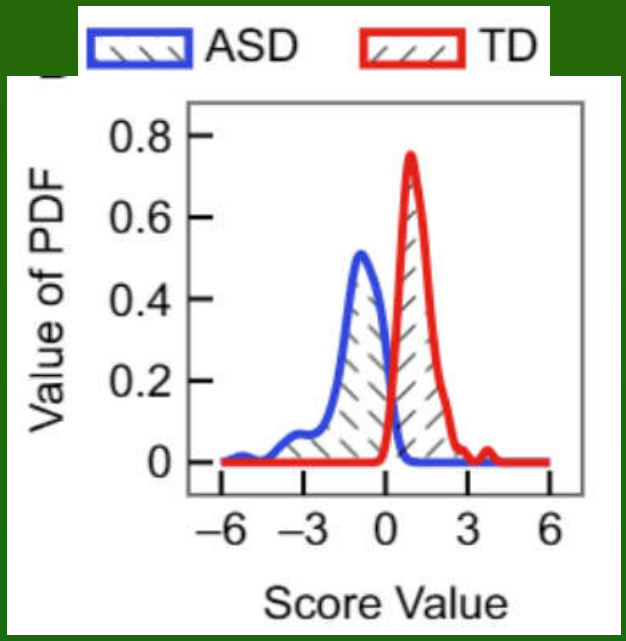
Metabolites in blood

ASD diagnosis based on metabolites in a blood sample: 88% correct.
D.P. Howsmon et al. Multivariate techniques enable a biochemical classification of children with ASD versus typically-developing peers: A comparison and validation study. Bioengineering & Translational Medicine, May 2018;

FOCM/TS metabolites were available for 154 (76% male) participants with ASD, age 8.8 years (range 2–17 years).

Score based on linear combination of 5 metabolites.

Only two studies so far, age effects are unknown, but potentially very early diagnostic possible.



Boys vs. girls

Why boys more often than girls?

Animal models of autism – some genes are deleted, mice and rats stop being social animals.

Differences in brain signaling pathway affect reward learning and motivation. Sex-specific differences in molecular signaling pathways are found in the striatum brain region.

Only male mice with the autism-associated genetic deletion have abnormal reward-learning behavior.

Female mice with the same genetic deletion are not affected.

N.M. Grissom et al. **Male-specific deficits in natural reward learning in a mouse model of neurodevelopmental disorders**. *Molecular Psychiatry* **23**, 544 (2018)

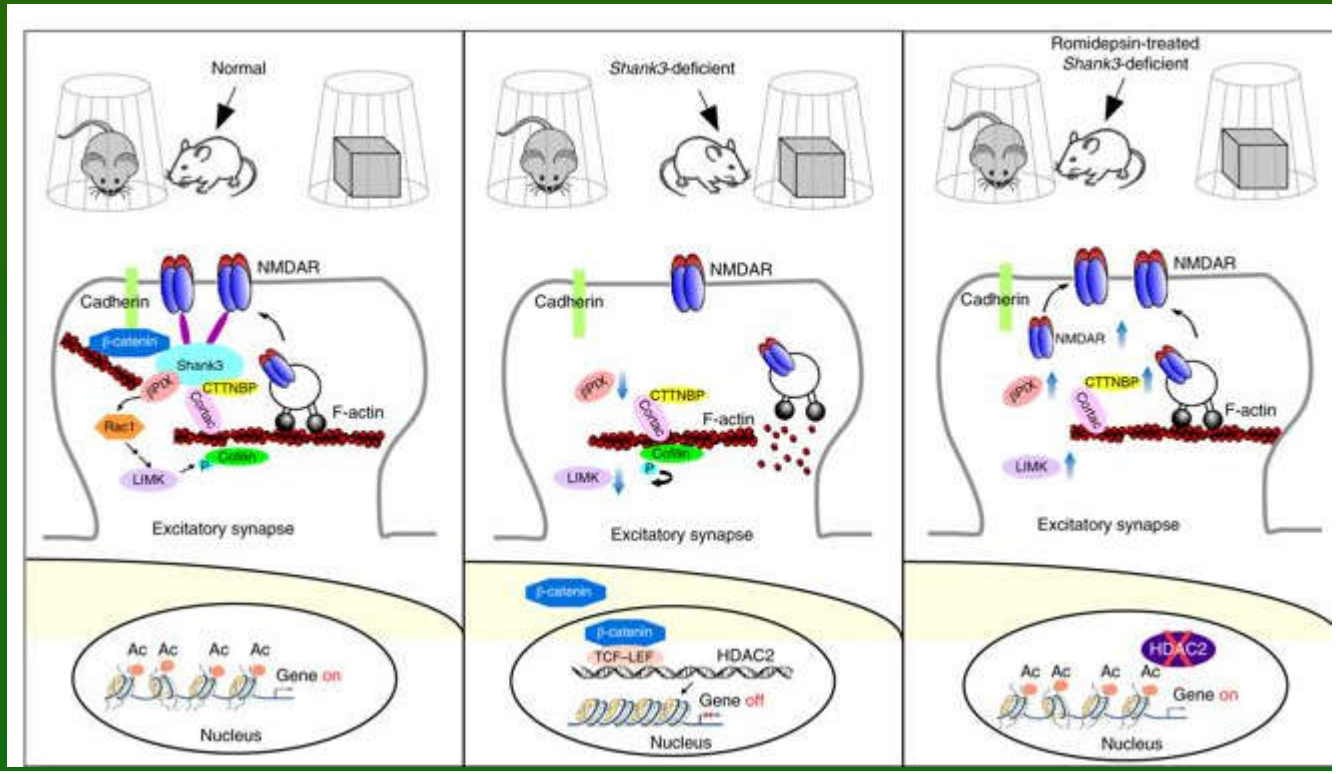
Epigenetics

Anti-cancer drug restored social deficits in animal models of autism in a sustained fashion! Brief treatment with a very low dose of **romidepsin**, affects many genes that are involved in neuronal communication.

Looses chromatin, exposes DNA, increases expression of genes.

Luye Qin et al. Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition. *Nature Neuroscience*, 2018.

Perhaps very early treatment may restore typical developmental pathways, but late applications will not remove underconnectivity effects easily.

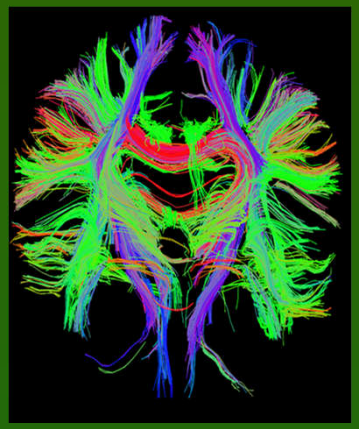


Brain structures & connections

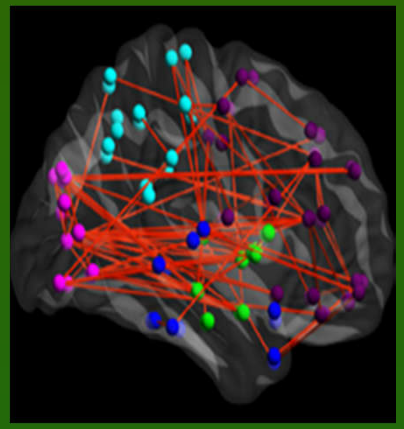
Human connectome and MRI/fMRI

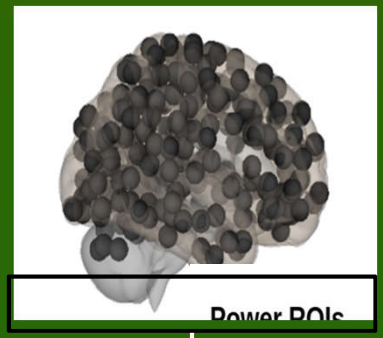
Node definition (parcelation)

Structural connectivity



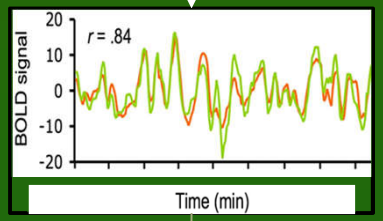
Functional connectivity



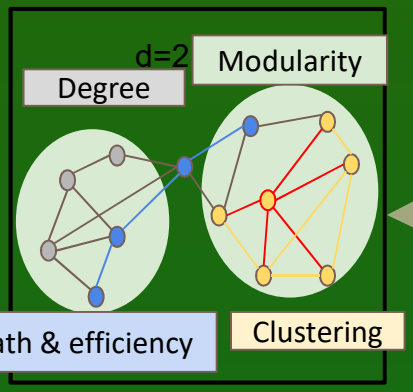


Signal extraction

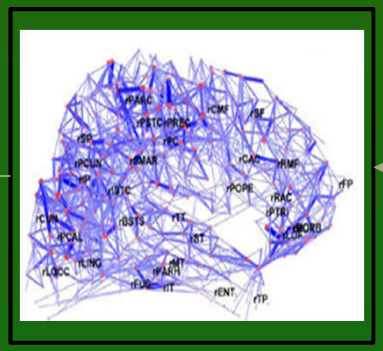
Correlation calculation



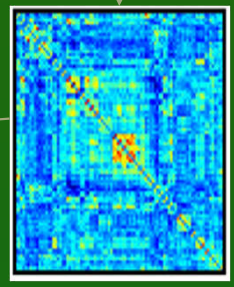
Graph theory



Whole-brain graph



Binary matrix

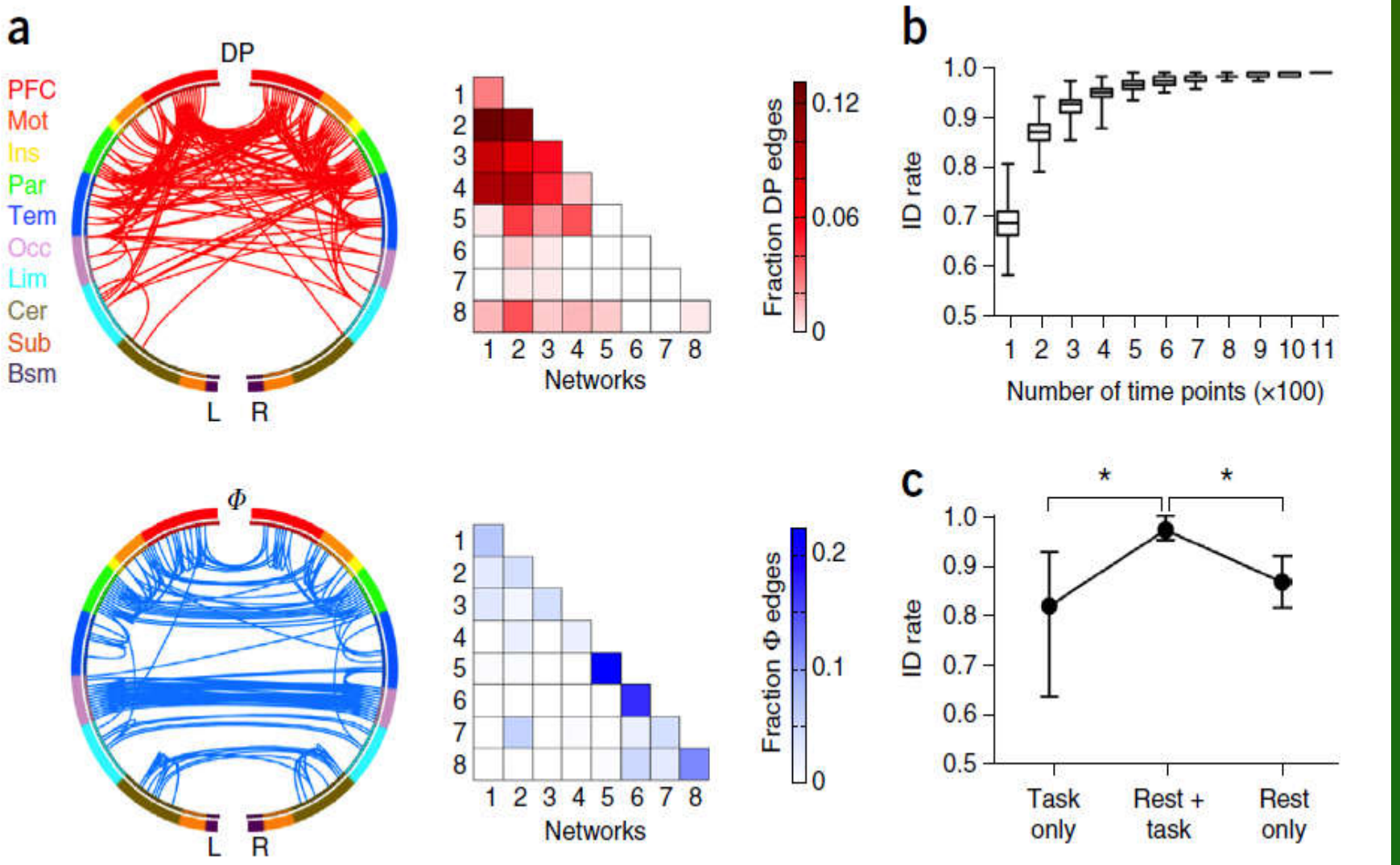


Correlation matrix

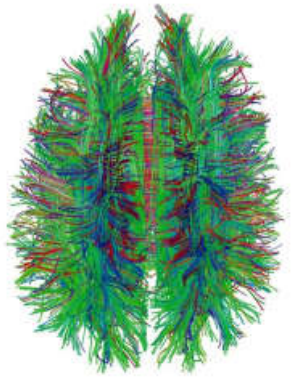
Many toolboxes available for such analysis.

Bullmore & Sporns (2009)

Finn et al. (2015), **Functional connectome fingerprinting**: identifying individuals using patterns of brain connectivity. Nature Neuroscience. Top: highly unique; Bottom: highly consistent connections.



Reduced functional connectivity



The underconnectivity theory of autism is based on following ideas:

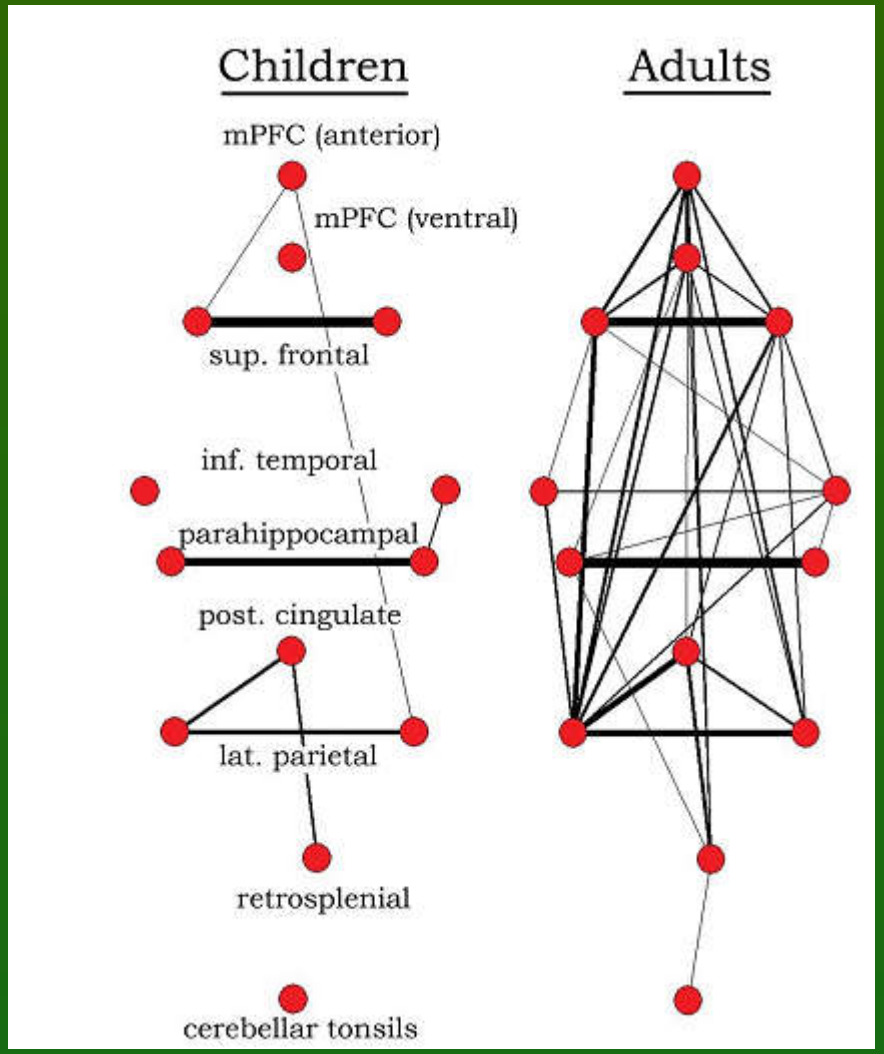
- Excess of low-level (sensory) processes - hyperspecificity.
- **Underfunctioning** of high-level neural connections and synchronization,
- fMRI and EEG study suggests that adults with ASD have local overconnectivity in the cortex and weak functional connections between the frontal lobe and the rest of the cortex.
- **Underconnectivity** is mainly within each hemisphere of the cortex, autism is seen as 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 always the case in autism.

Connectome development

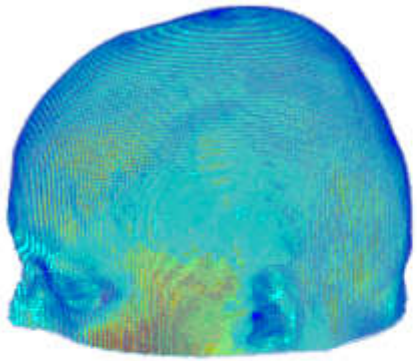
External stimulation should evoke changes of internal brain states, otherwise connections will not form.

Low-level (sensory) processes may trap attention leading to stimulation of sensory cortices, but not the whole network.

Developmental effect: underconnectivity.



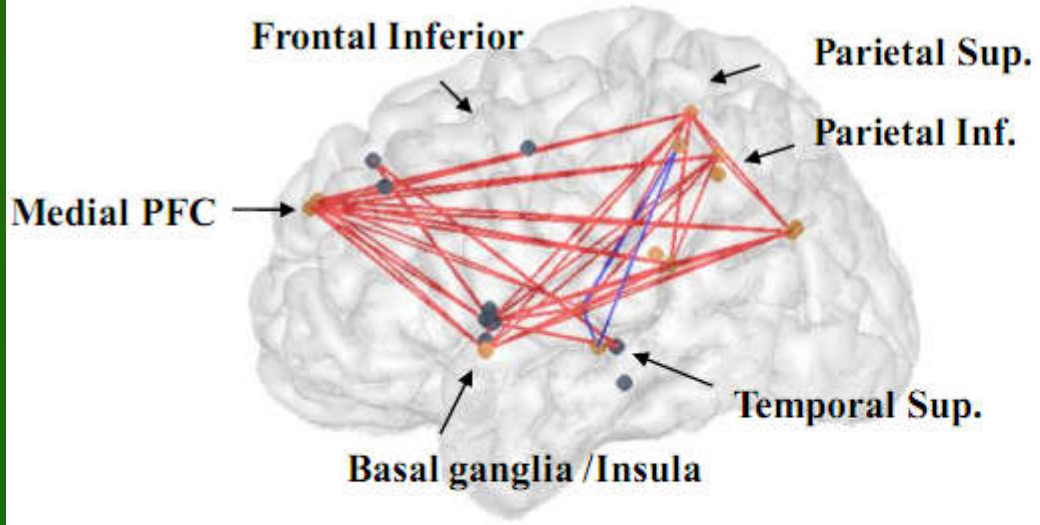
Head position



Connectivity : 63 ROI analysis

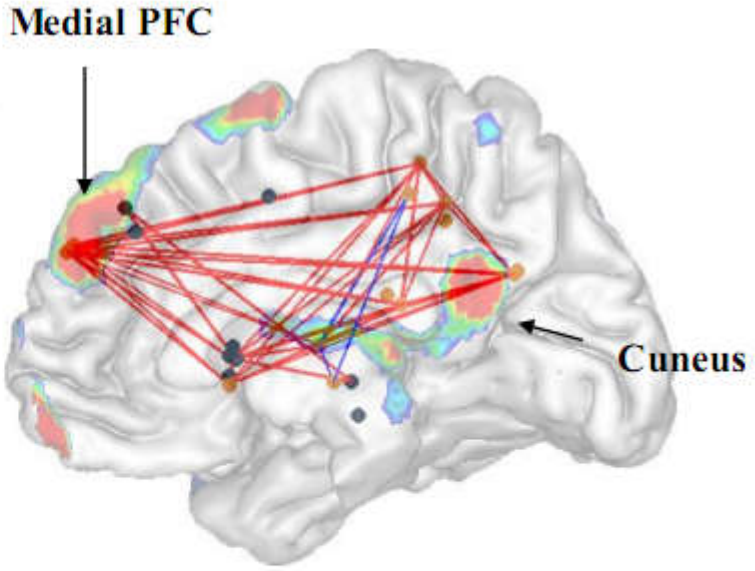
Significant in ASD not in Controls

Significant in Controls, not in ASD



Region of the default mode network

Region of the active network



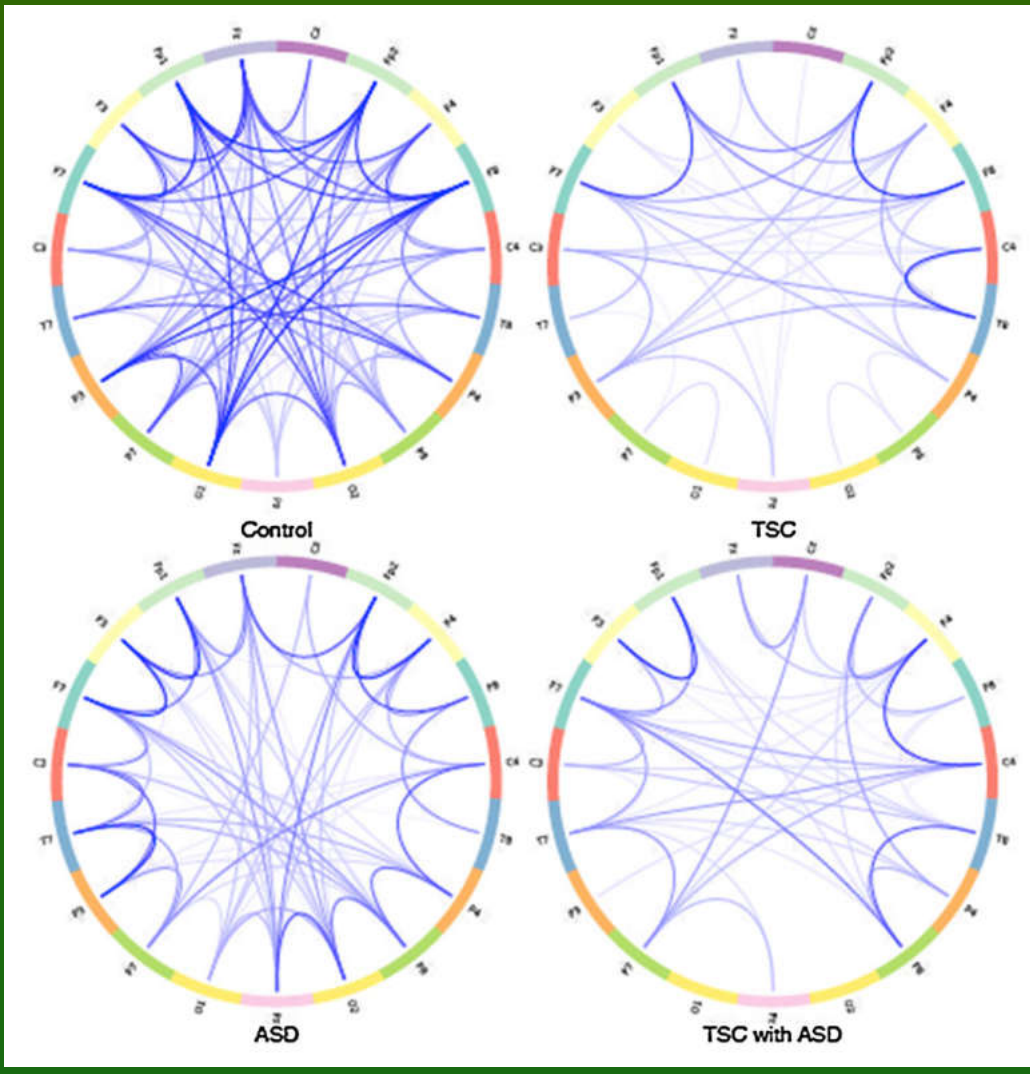
Brain activations in the FMRI experiment on emotion perception

ASD: pathological connections

Comparison of connections for patients with ASD (autism spectrum), TSC (Tuberous Sclerosis), and ASD+TSC.

Coherence between electrodes. Weak or missing connections between distant regions prevent ASD/TSC patients from solving more demanding cognitive tasks.

Network analysis becomes very useful for diagnosis of changes due to the disease and learning; **correct your networks**!

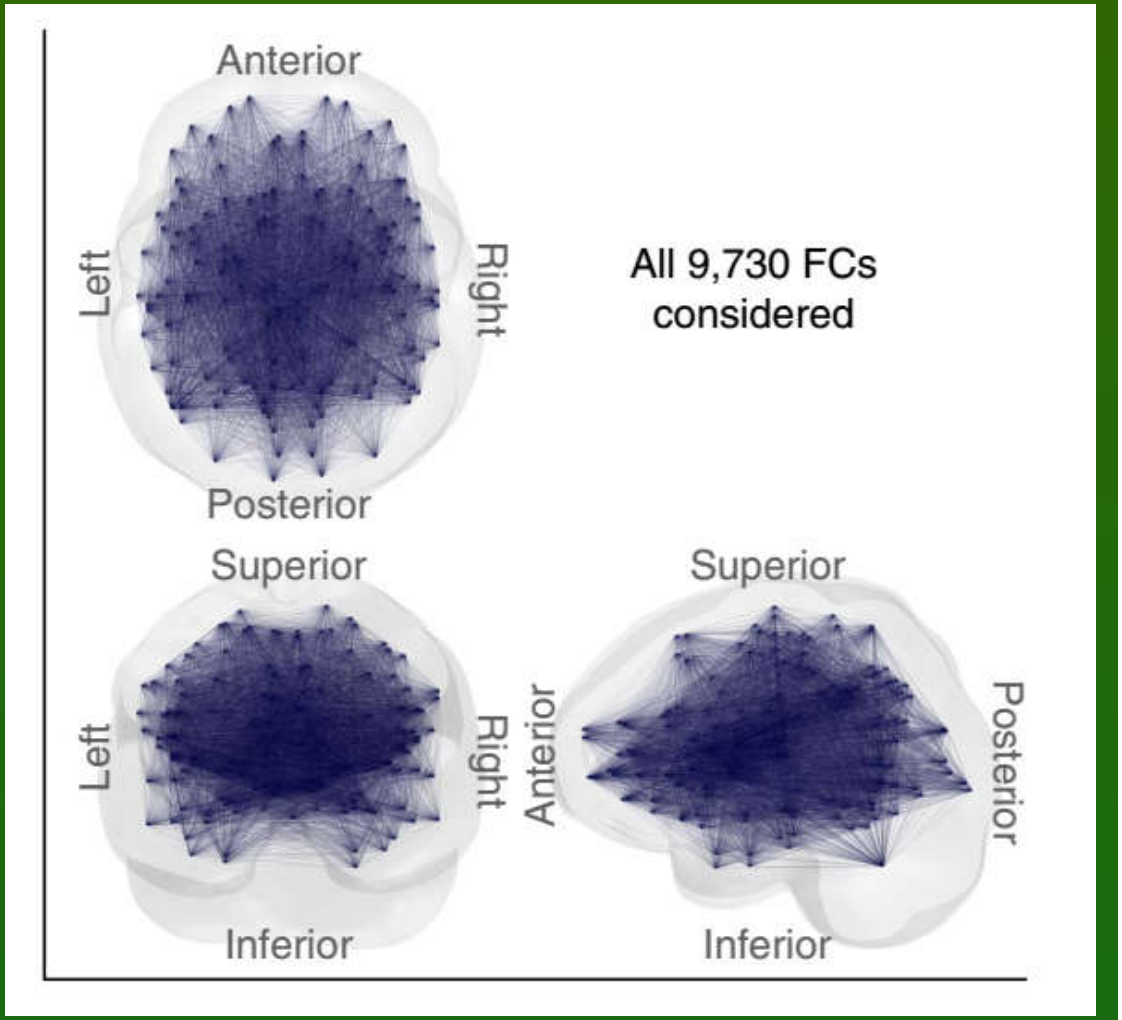


J.F. Glazebrook, R. Wallace, Pathologies in functional connectivity, feedback control and robustness. Cogn Process (2015) 16:1–16

ASD connectome

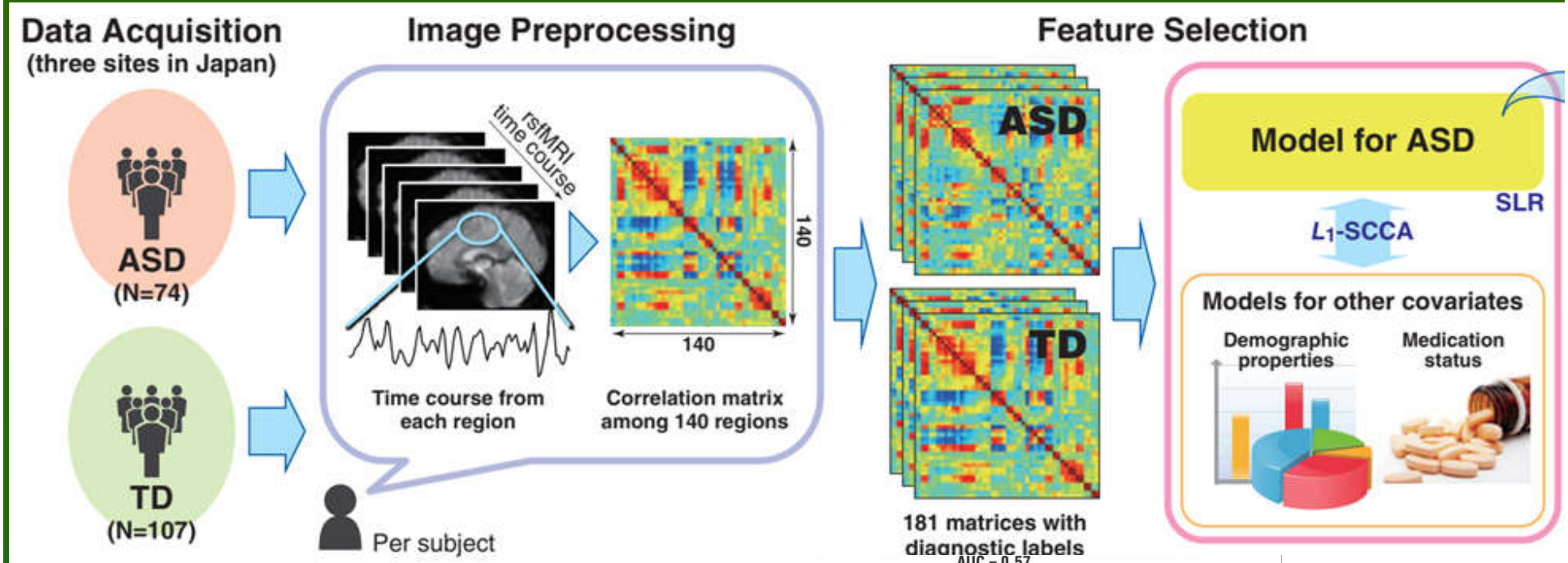
Analysis of functional connections (using Brain Connectivity Toolbox) between brain regions measured using fMRI in the resting state between 140 ROIs leads to 9730 possible functional interactions (direction not distinguished).

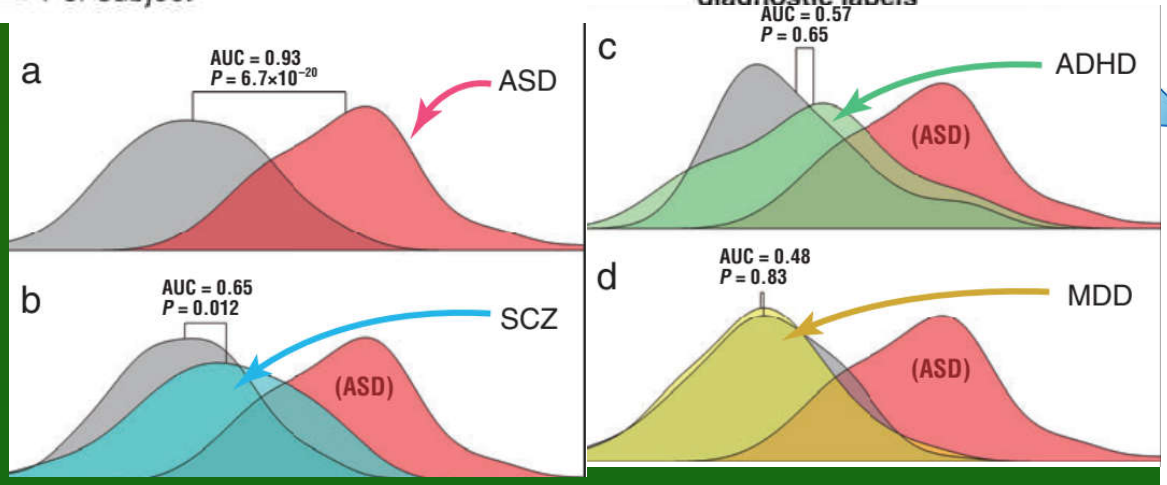
Selecting the most important 16 connections classification accuracy of 85% was reached, distinguishing ASD people form the healthy ones.

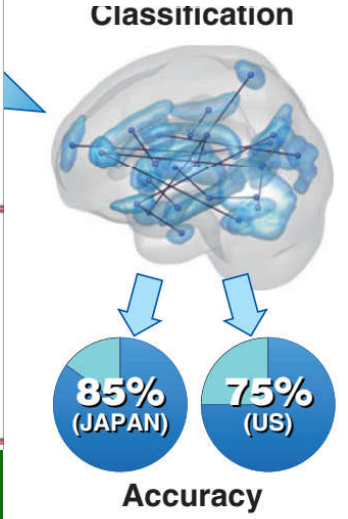


N. Yahata et al., A small number of abnormal brain connections predicts adult autism spectrum disorder. Nature Communications (2016)

Diagnosis based on fMRI

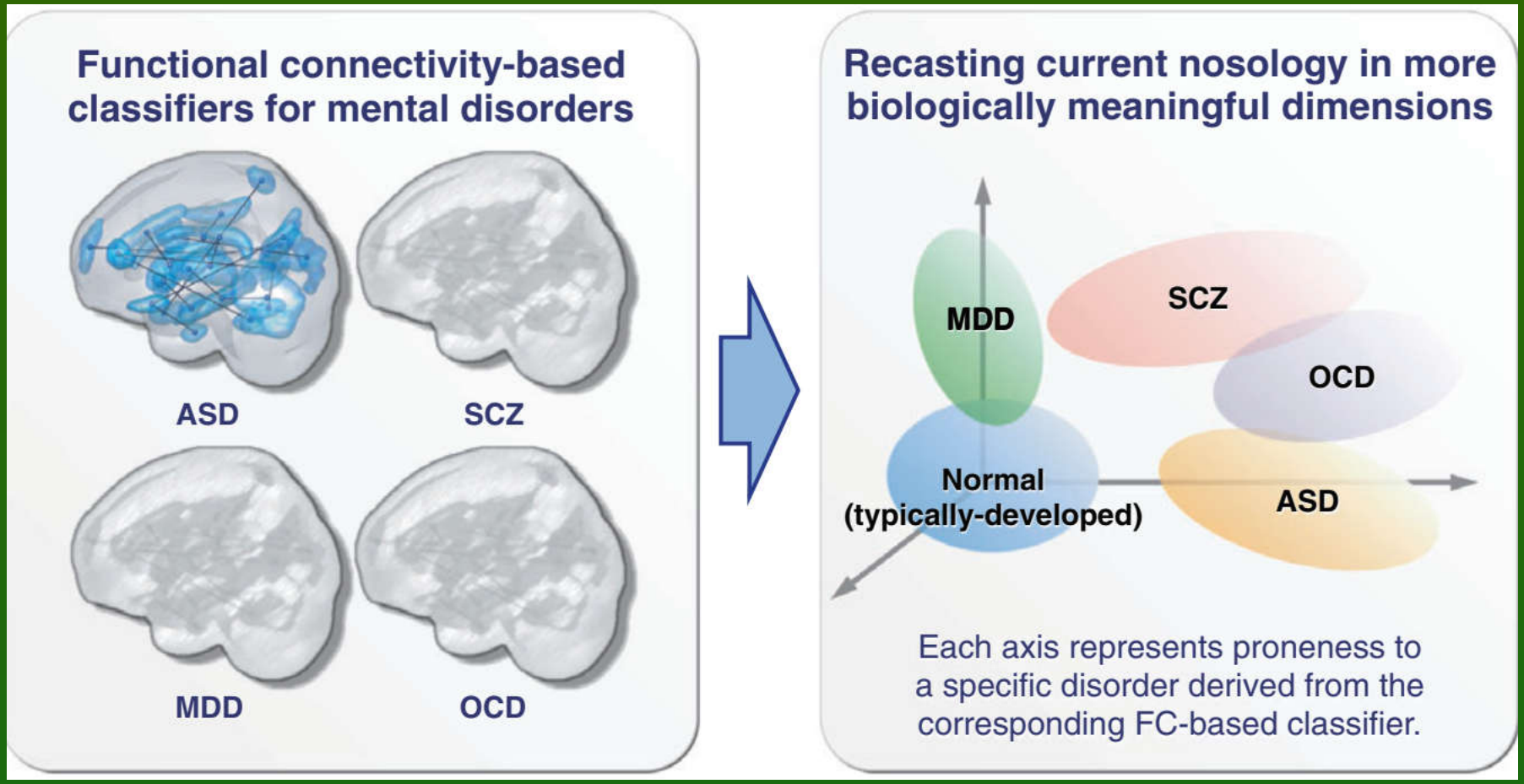






N. Yahata et al, *Psychiatry and Clinical Neurosciences* 2017: **71**

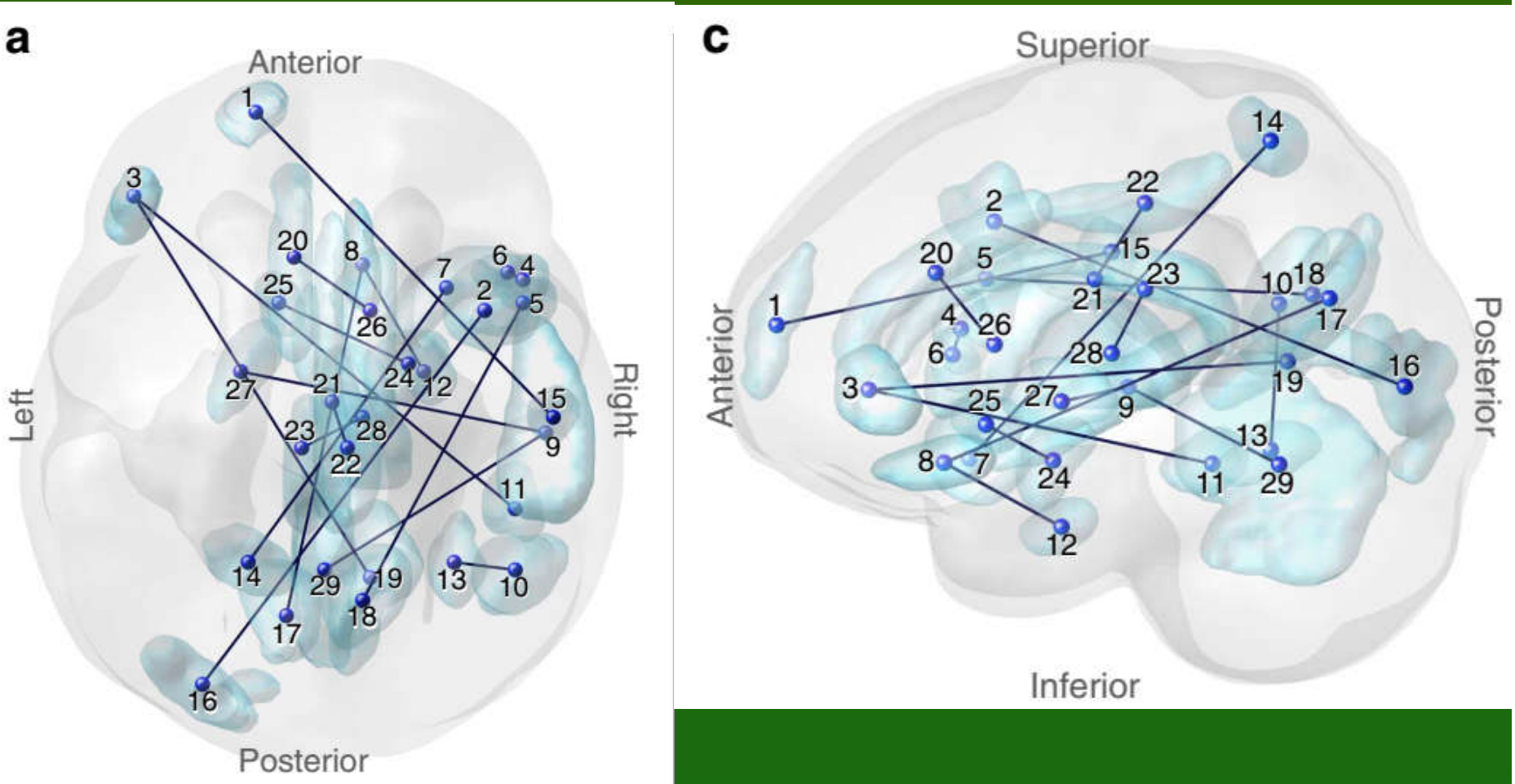
Proneness to 4 disorders



MDD, major depressive disorder, SCZ, schizophrenia, OCD, obsessive compulsive disorder, in ASD and SCZ axis.

N. Yahata et al, *Psychiatry and Clinical Neurosciences* 2017; **71**: 215–237

Selected connections



N. Yahata et al, *Nat. Commun.* 2016. 29 selected regions (ROI) and 16 connections were sufficient to recognize ASD with 85% accuracy in 74 Japanese adult patients vs. 107 people in control group; without re-training accuracy was 75% on US data.

PINT

Personalized Intrinsic Network Topography (PINT).

ABIDE network, (Autism Brain Imaging Data Exchange), enabling a large sample of 393 people with autism and 496 as a comparison group.

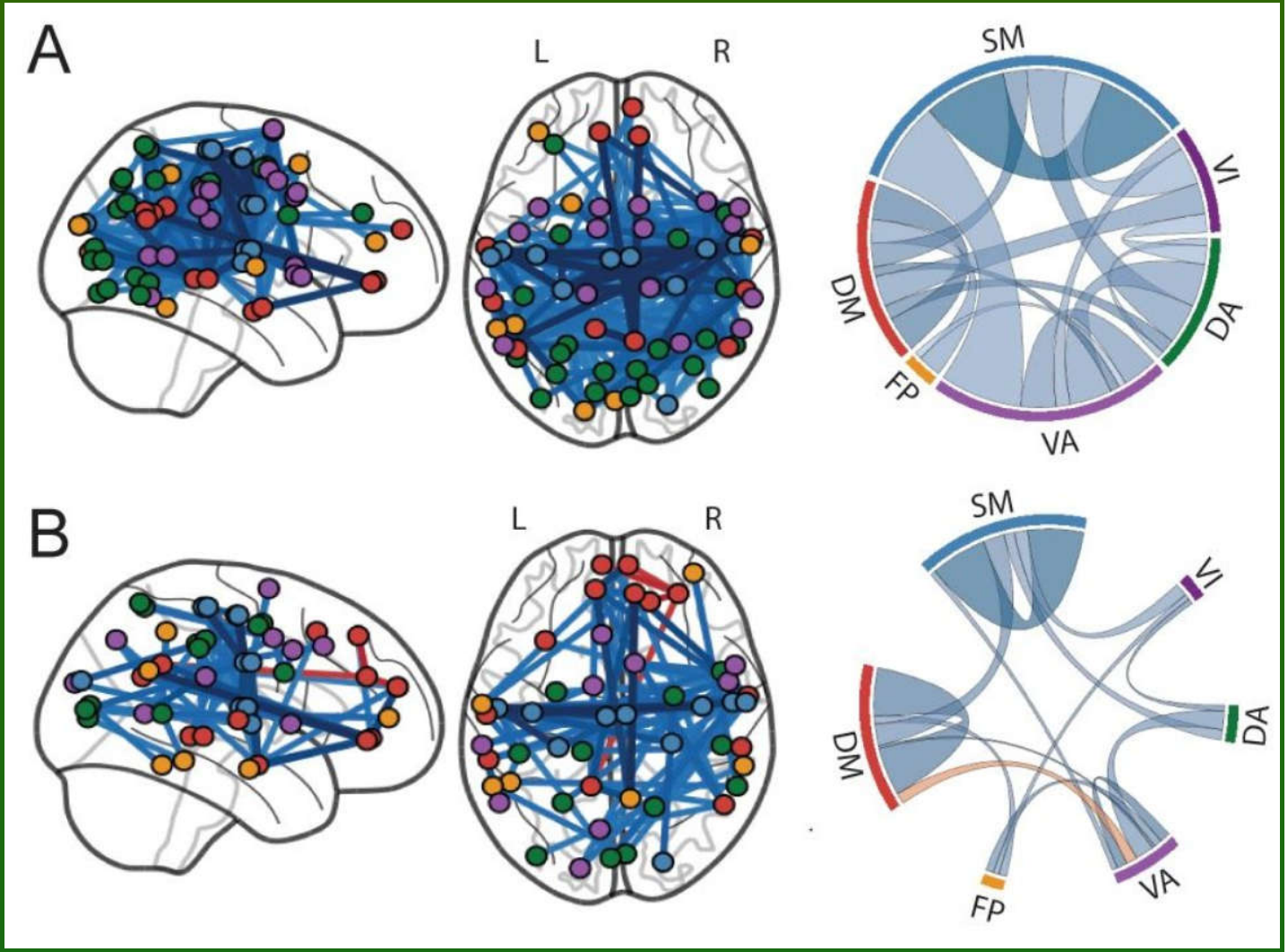
Brain networks related to attention in autism may not only be disconnected, but also displaced. Resting-state networks within individuals with ASD compared with those in TD individuals shows greater variability in the spatial locations. For TD persons, variability decreased from childhood into adulthood and increased in late life, following a U-shaped pattern not present in ASD.

Analysis using PINT leads to a smaller number of underconnected regions in ASD, from 214 to 80 connections; better selection.

E.W. Dickie et al. Personalized Intrinsic Network Topography Mapping and Functional Connectivity Deficits in Autism Spectrum Disorder. *Biological Psychology* 3/2018.

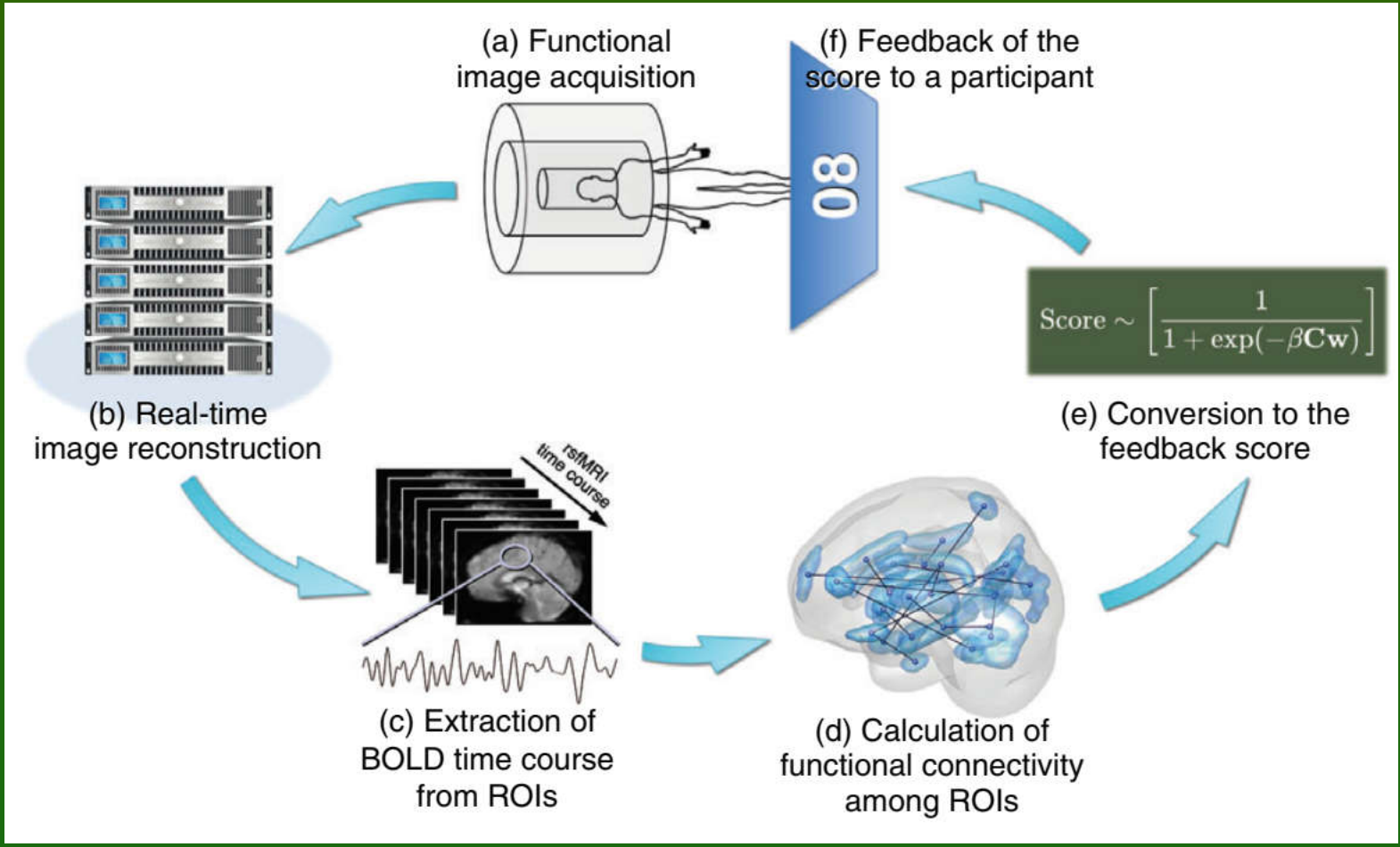
PINT

Locations and chord diagram of network composition.
214 edges showing significant hypo-connectivity in ASD.
After PINT, the # of significant hypo-connected edges (blue) is reduced to 80 and 4 hyper-connectivity connected (orange) edges are seen.



The width of the chord represents the number of significant edges and color of the chord represents the mean effect size for those significant edges.

Neurofeedback may repair network?



Megumi F, Yamashita A, Kawato M, Imamizu H. Functional MRI neurofeedback training on connectivity between two regions induces long-lasting changes in intrinsic functional network. *Front. Hum. Neurosci.* 2015; **9**: 160.

Restoring stronger information flow

- Increase neuroplasticity using Transcranial Magnetic Stimulation.
- Train using task requiring cooperation of selected brain areas.
- Use High-Density Direct Current stimulation to speed learning.

Pharmacology?

NitroSynapsin compound improves synapse function, 'network' communication in the brain. Eventually it may help several neurological diseases.

So far good results are achieved in MEF2C Haploinsufficiency Syndrome (MHS) in mice, preliminary evidence for human MHS.

Shichun Tu et al. **NitroSynapsin therapy for a mouse MEF2C haploinsufficiency model of human autism**. *Nature Communications*, 2017; 8 (1)

Diagnostic breakthroughs?

EEG 3 month old

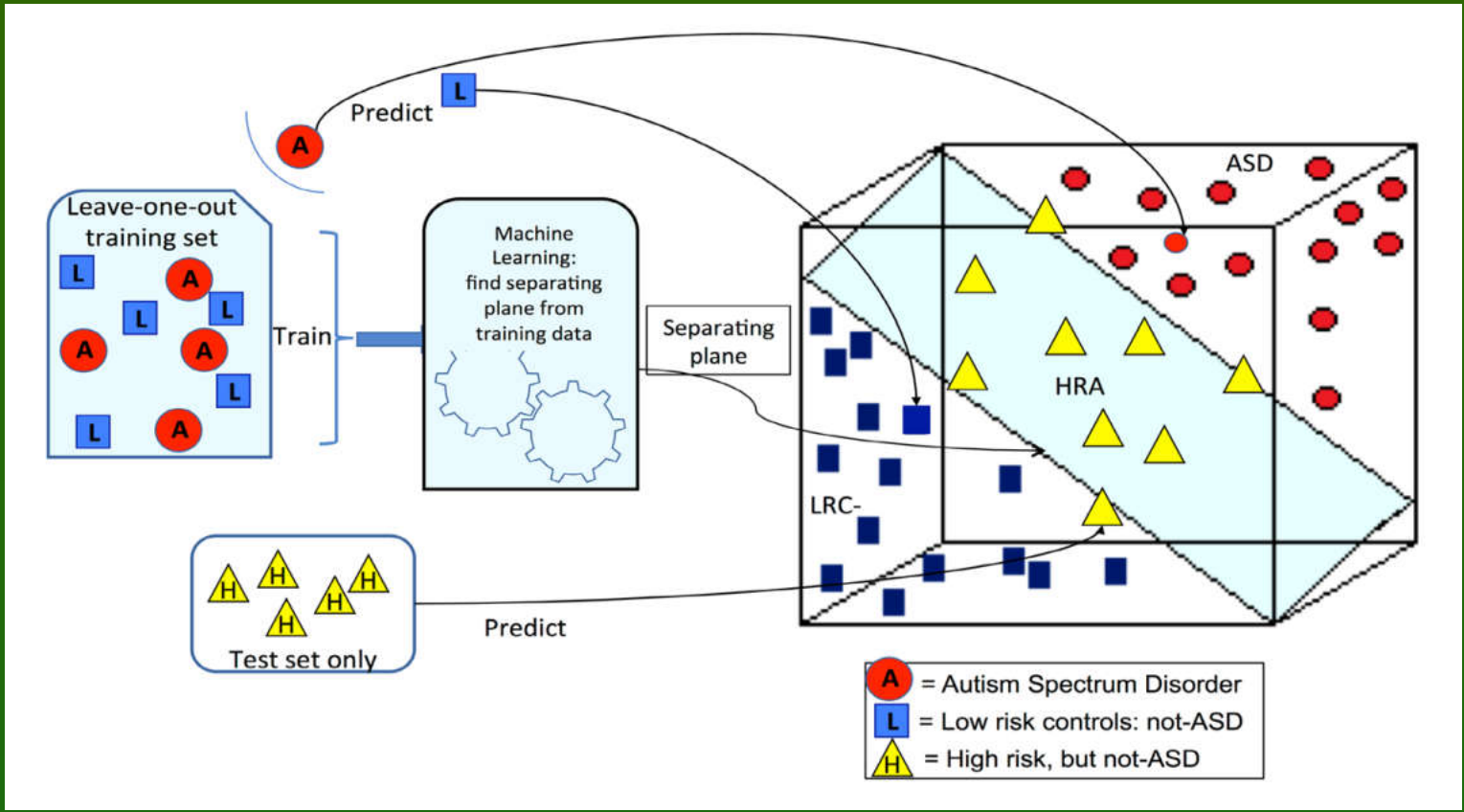
Bosl, W. J., Tager-Flusberg, H., & Nelson, C. A. EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach. *Scientific Reports*, *8*(1), 6828 (2018).

19 electrodes selected, children 3-36 month old, ASD predicted with ~ 95% success …

Features: not only structure but dynamics.
Nonlinear invariant measures of a time series and their physical interpretation, recurrence quantification analysis (RQA). For example:

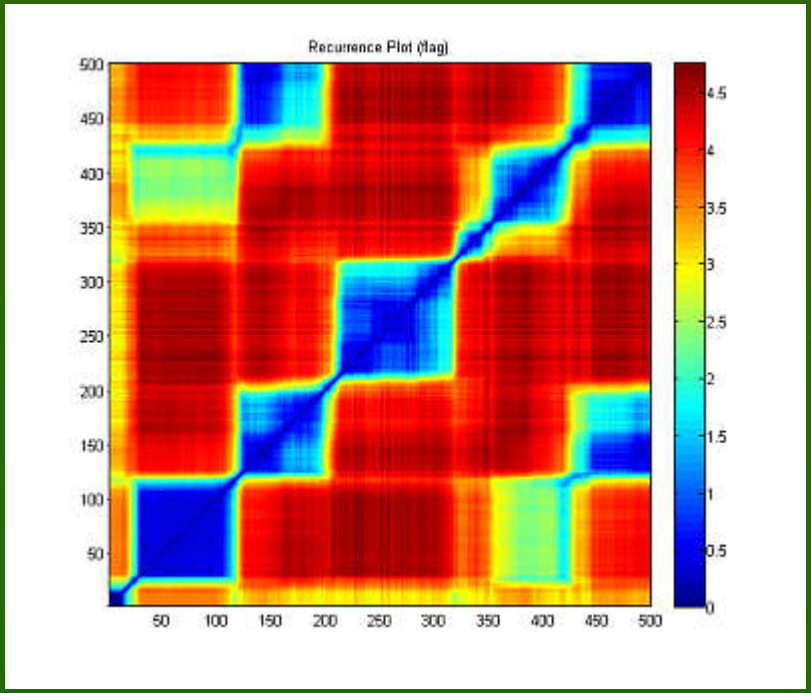
1. Sample Entropy (SampE)
2. Entropy derived from recurrence plot (L_entr).
3. Recurrence rate (RR), probability of recurrence.
4. Determinism (DET), repeating patterns in the system.
5. Laminarity (LAM), frequency of transitions between states.
6. Trapping time (TT), time in a given state.

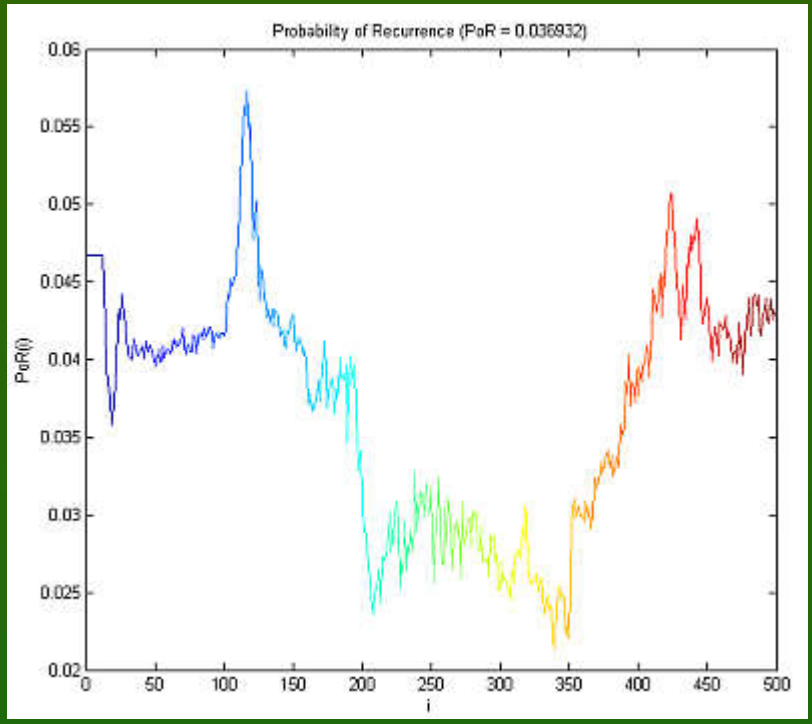
ASD EEG SVM Classification



Wavelet decomposition, Recurrent Quantification Analysis, feature ranking and machine learning. Nonlinear features are critical to achieve good results, and their correlated with ASD depends on age.

Probability of recurrence

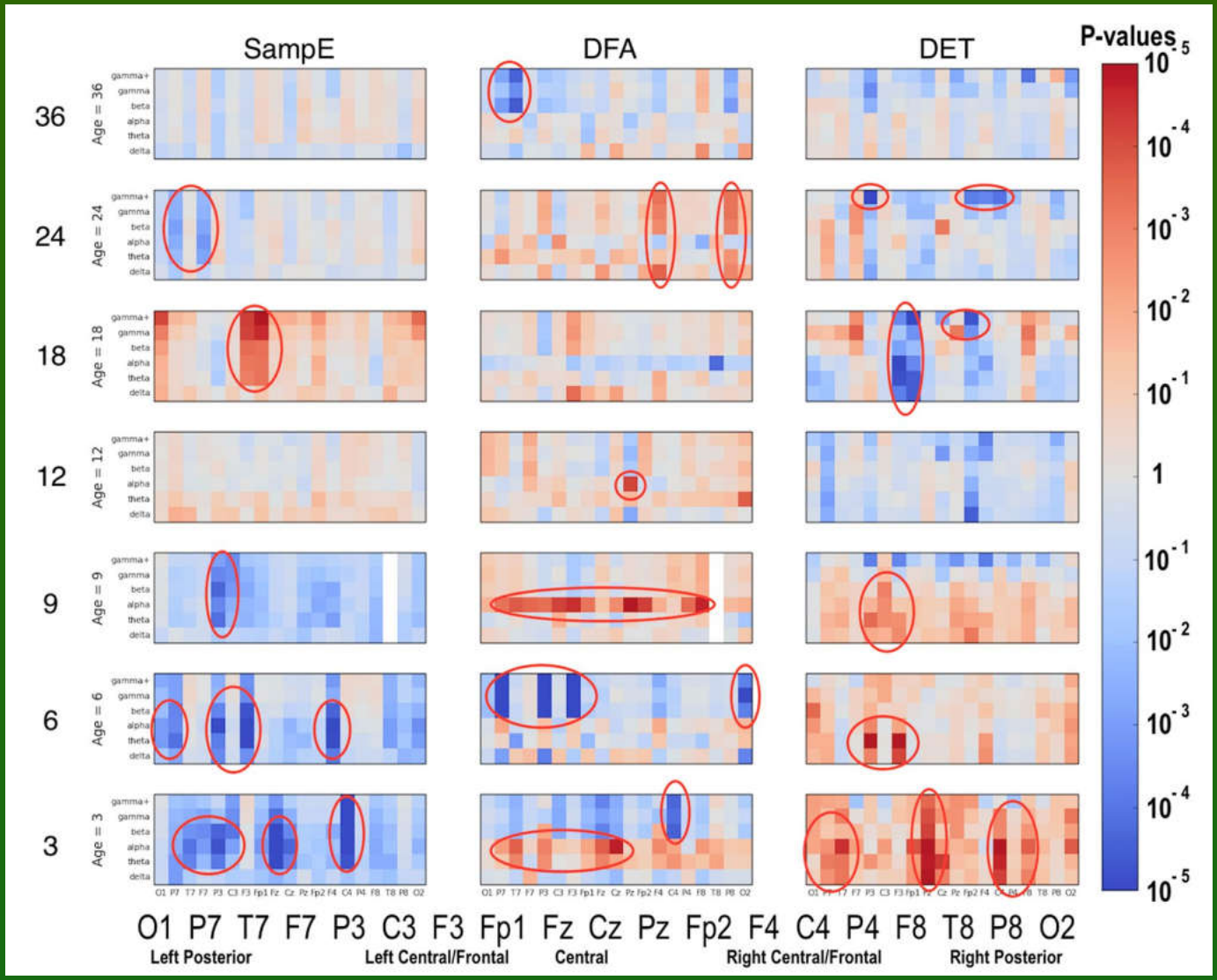




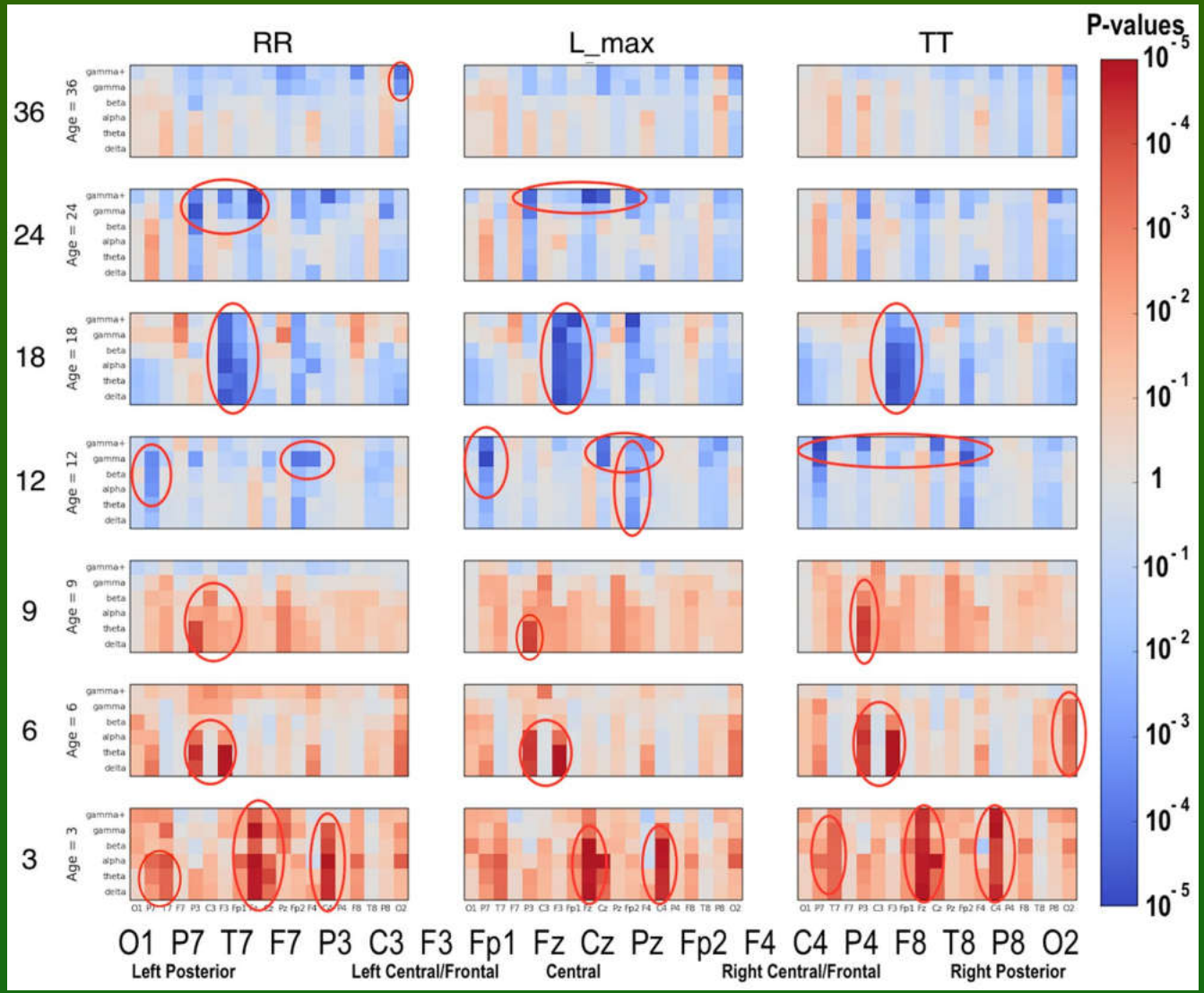
Probability of recurrence may be computed from recurrence plots, or from clusterization of trajectory points, allowing for evaluation how strongly some basins of attractors capture neurodynamics.

Our Viser Toolbox is used for all visualizations

ASD EEG Features



ASD EEG Features

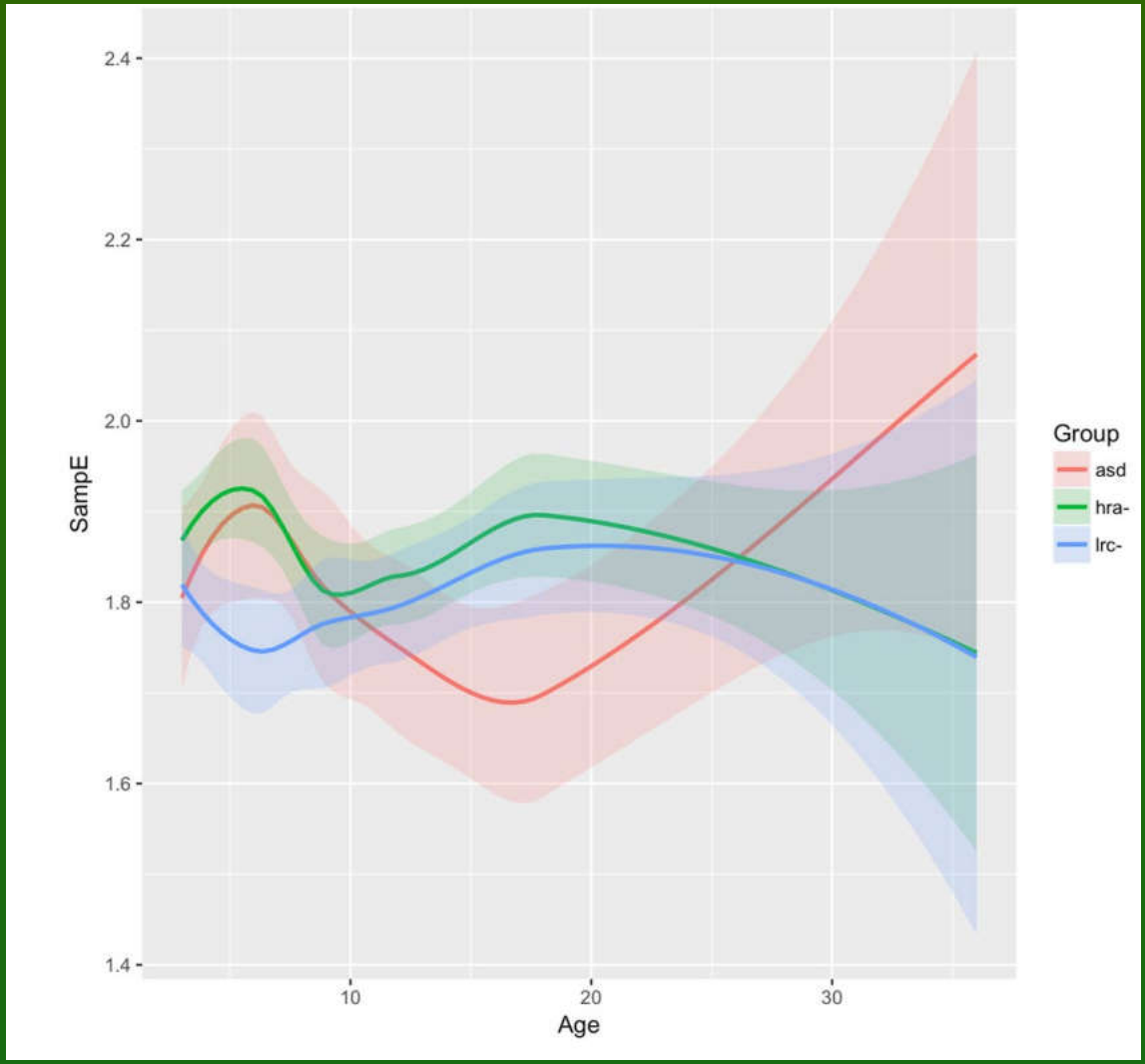


ASD EEG SVM Classification

Developmental trajectories for SampE in the left temporal region (T7 sensor) in higher frequencies (beta+gamma) for ASD, LRC-, and HRA-

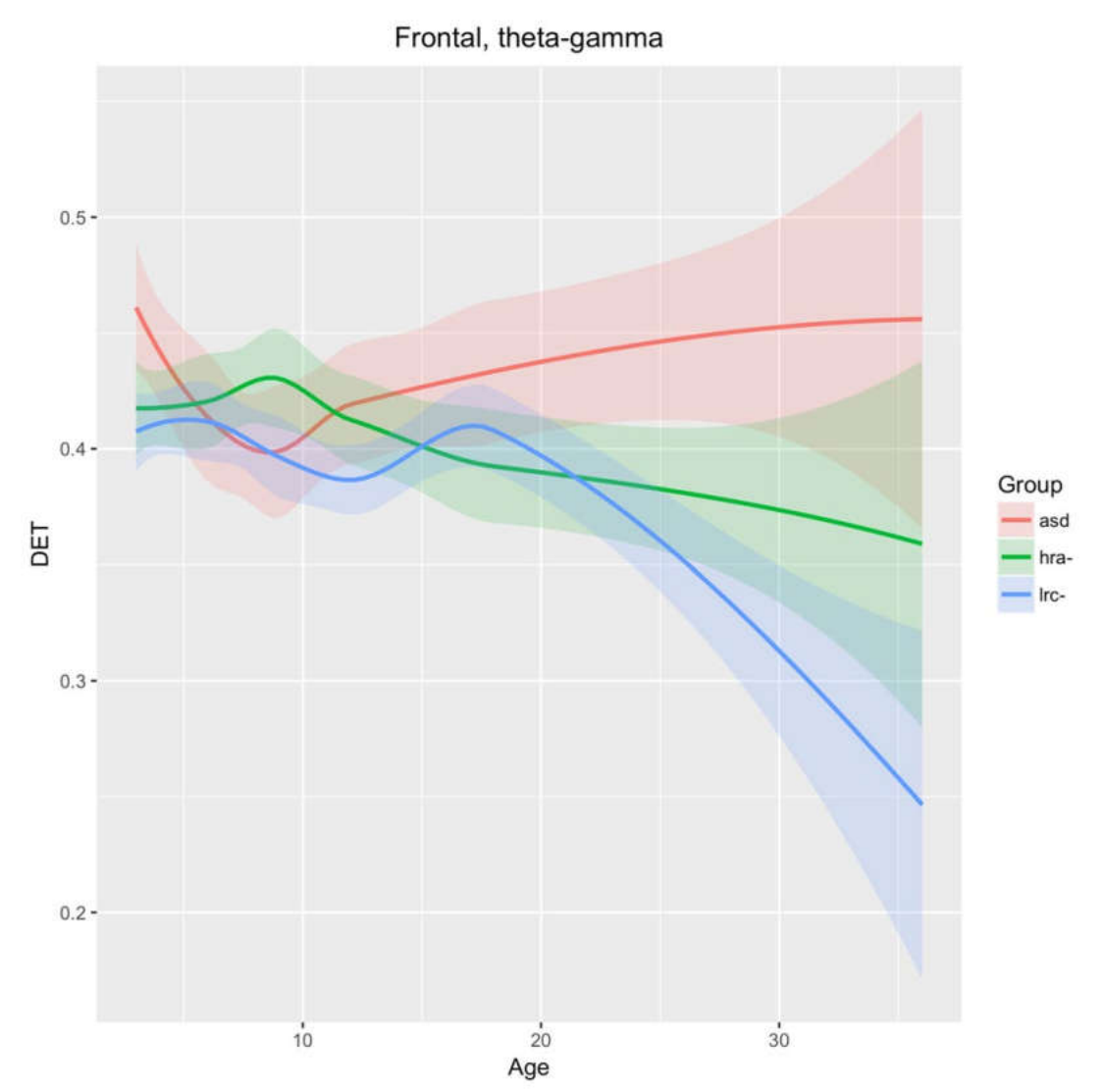
LRC low risk controls

HRA high risk for ASD - no ASD



ASD EEG SVM Classification

Developmental trajectories for DET in the entire frontal region (Fp1 +F7+Fz+F8+Fp2 sensors)
in higher frequencies (beta +gamma) for ASD, LRC-, and HRA-.



Head movements

Low Risk (LR) 1–2 month old infants' movements were significantly different during a language listening task compared to during sleep.
HR infants' movements were more similar during both conditions.

Delays in early learning developmental trajectories in High Risk infants (validated in an analysis of 1,445 infants from representative infant-sibling studies) were predicted by worse stochastic patterns in their spontaneous head movements as **early as 1–2 months after birth**, relative to HR infants who showed more rapid developmental progress, as well as relative to all LR infants.

Inflexible sensorimotor systems and/or atypical transition between behavioral states may interfere with the establishment of capacity to extract structure and important cues from sensory input at birth, preceding and contributing to an atypical brain developmental trajectory in toddlerhood.

K. Denisova, & G. Zhao, Inflexible neurobiological signatures precede atypical development in infants at high risk for autism. Scientific Reports (2017)

Insights from computational models

Computational Models

Models at various level of detail.

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

Models of attention:

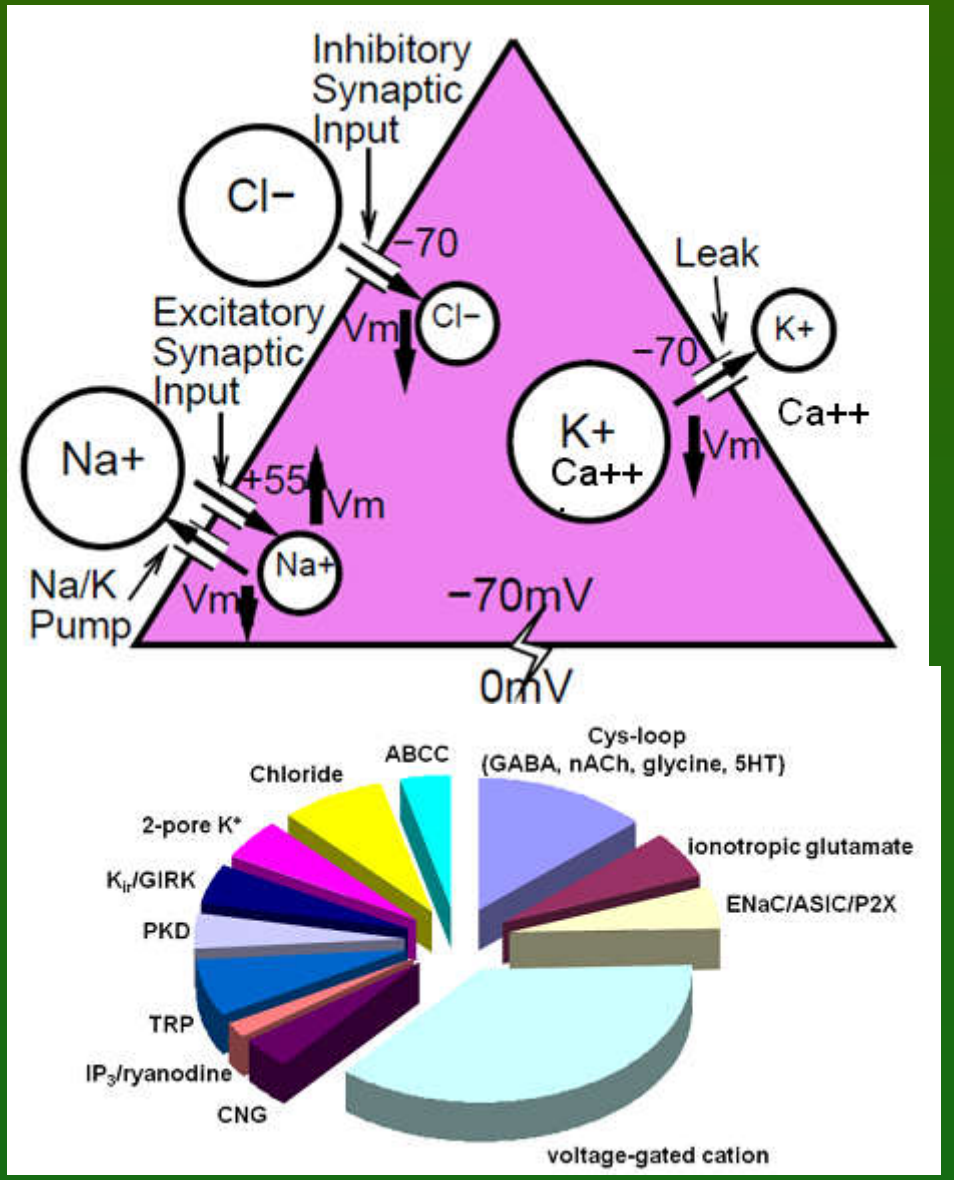
- Posner spatial attention;
- attention shift between visual objects.

Models of word associations:

- sequence of spontaneous thoughts.

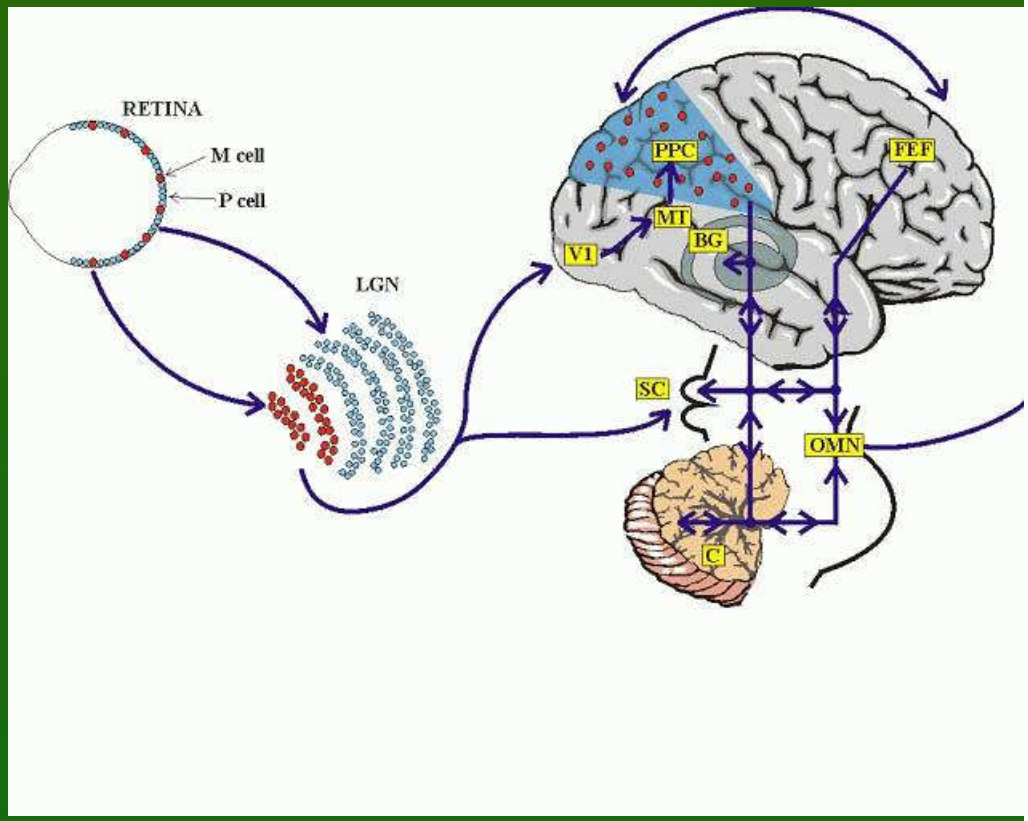
Models of motor control.

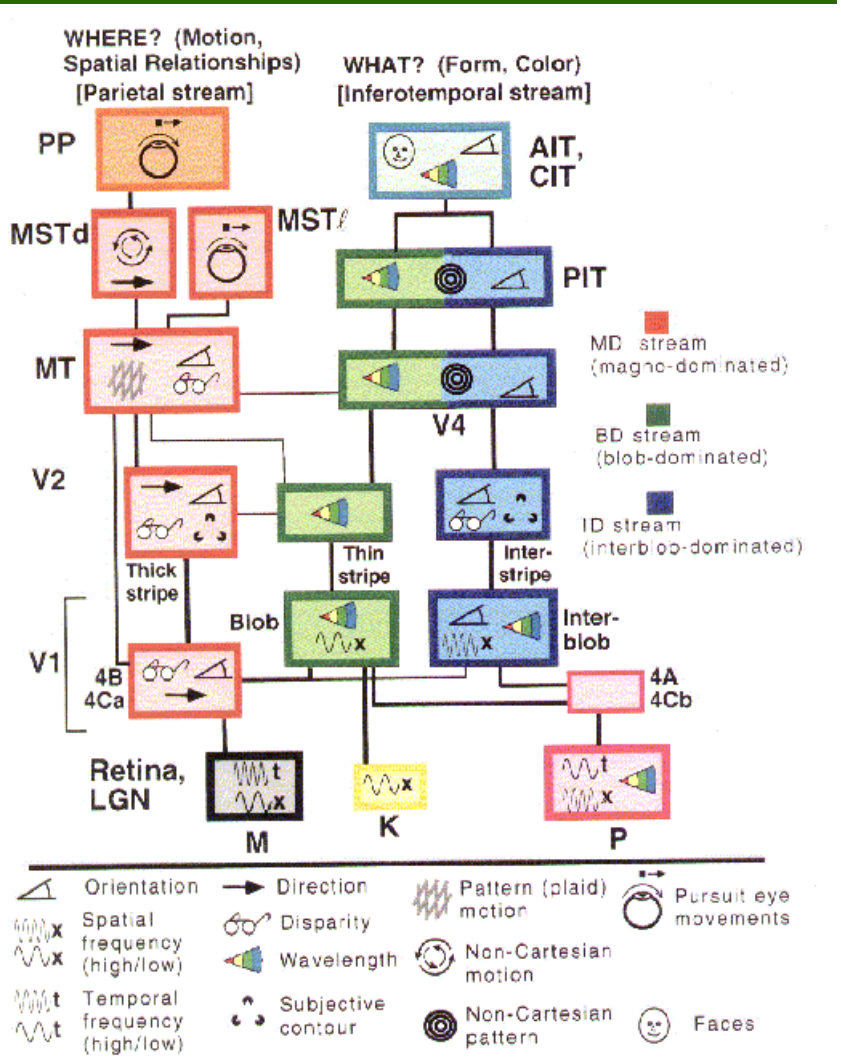
Critical: control of the increase in intracellular calcium, which builds up slowly as a function of activation.
Initial focus on the leak channels, 2-pore K^+, looking for genes/proteins.



Vision

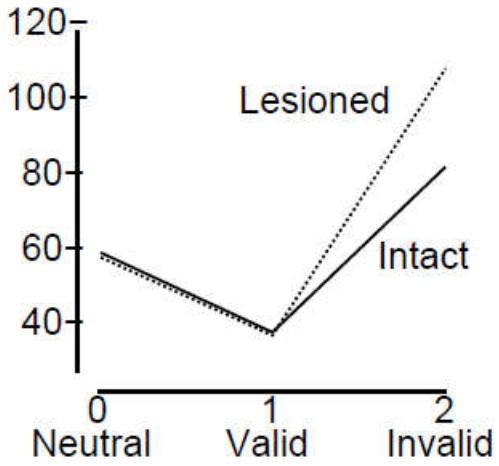
From retina through lateral geniculate body, LGN (part of thalamus) information passes to the primary visual cortex V1 and then splits into the ventral and dorsal streams.

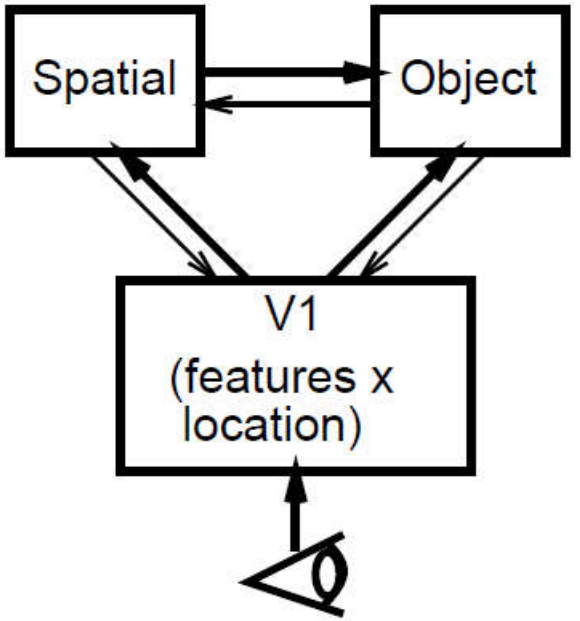




Posner visual orientation task

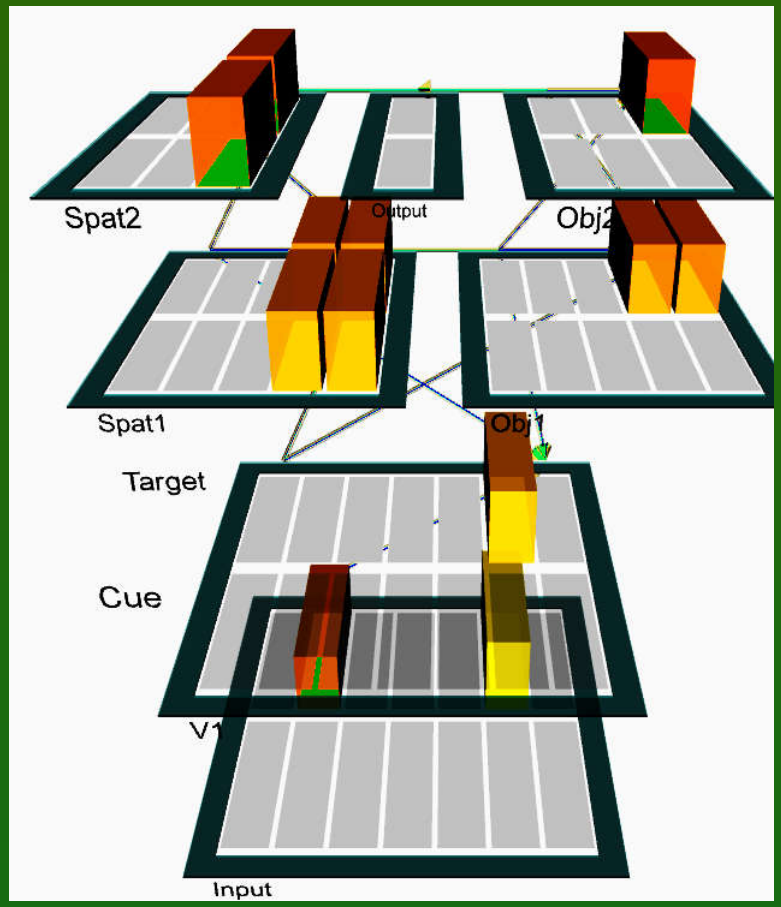
Cue (bright box) is in the same position as target (valid trial), or in another position (invalid trial), or there is no cue (neutral), just target.
Test of the object recognition/localization.



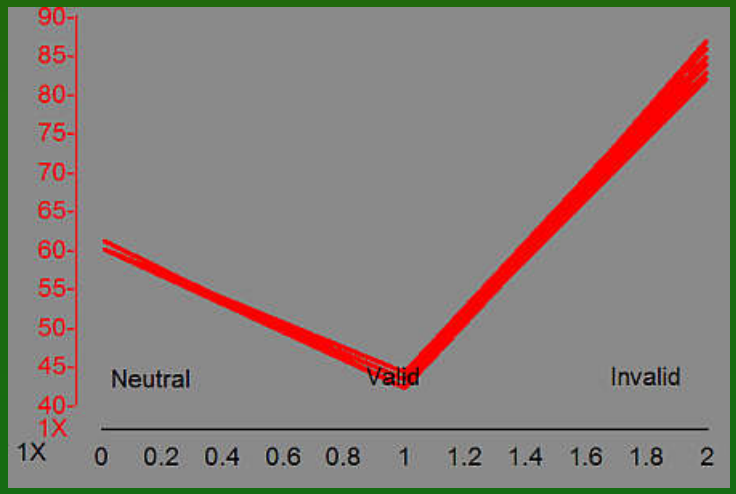


Posner spatial attention

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	



Recognition of many objects

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

Two objects are presented.

Connectivity of these layers:

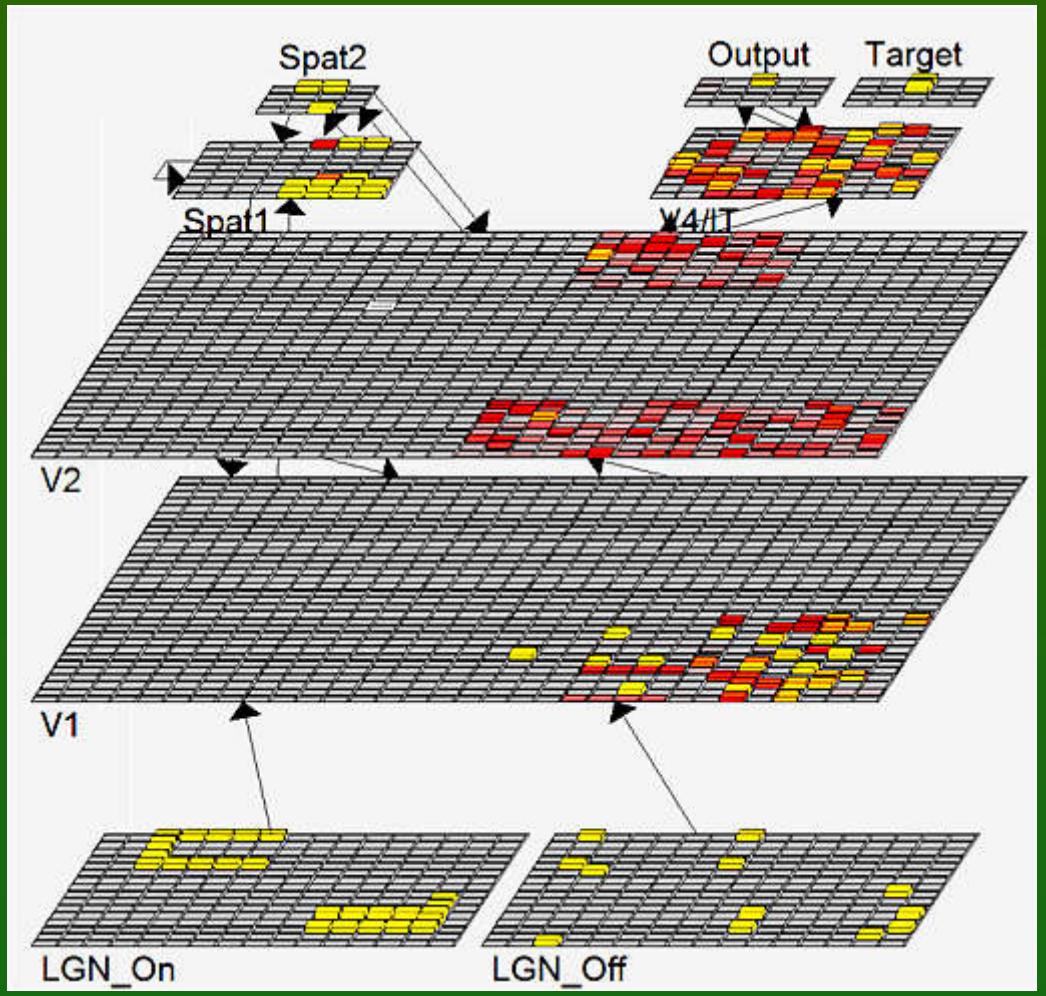
Spat1 ⇔ V2, Spat 2

Spat1 ⇔ V2, Spat 2

Spat2 ⇔ V2.

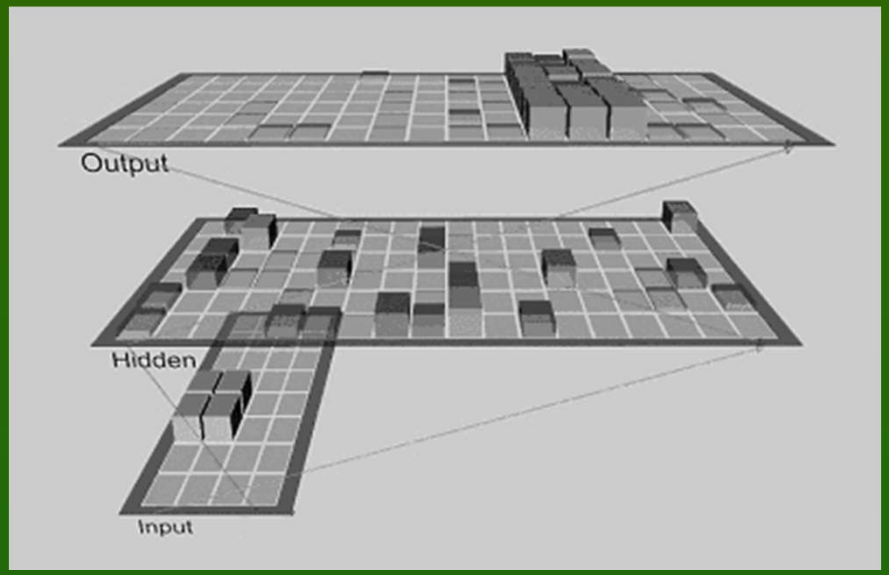
Spat1 has recurrent activations and inhibition, focusing on a single object.

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

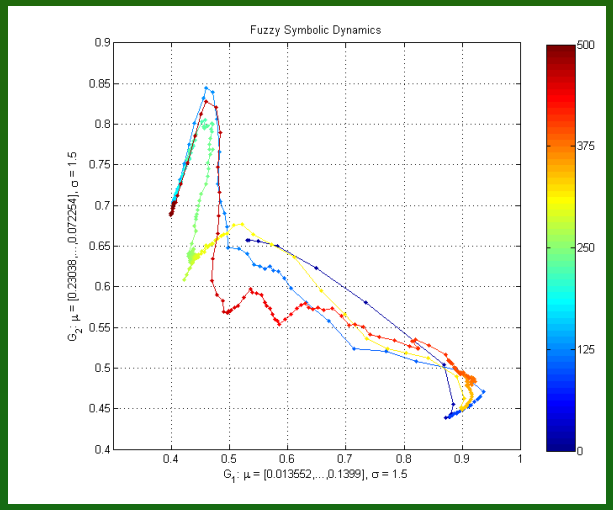


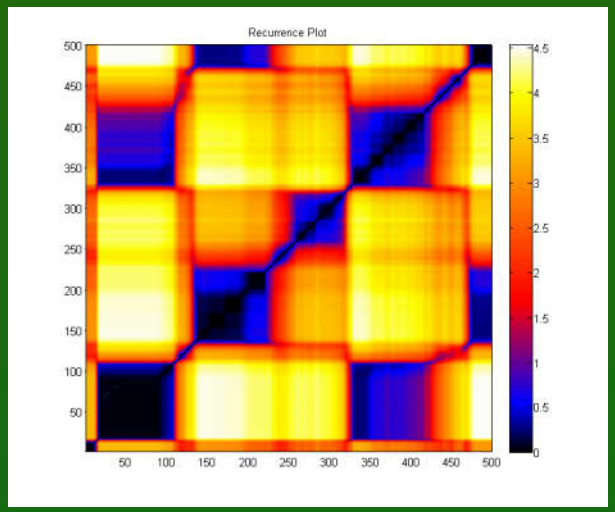
Model of movements

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.





Model of reading

Spontaneous transitions.

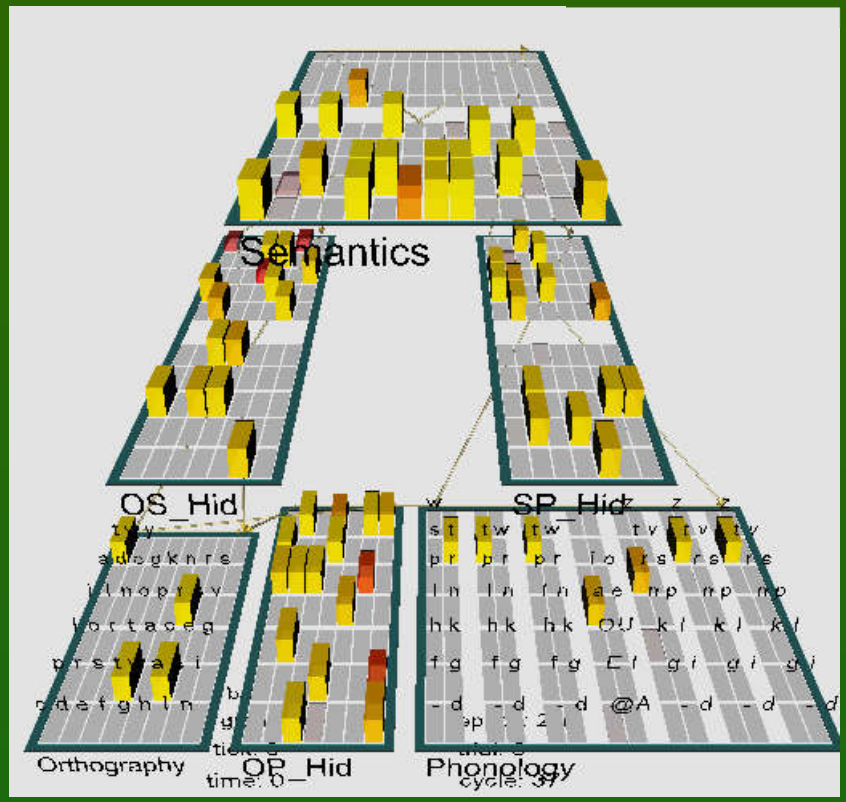
Emergent neural simulator:

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

3-layer model of reading:

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

Hidden layers in between.



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

Fluctuations around final configuration = attractors representing concepts.

How to analyze properties of attractor basins, their relations?

Neurodynamics

Trajectories show spontaneous attention shifts that emerge as a property of neurodynamics, and depends on:

- **synaptic connections**: local connectivity, inhibitory competition, bidirectional inter/intralayer processing, multiple constraint satisfaction …
- **neural properties**: thresholds, accommodation, exc/inh/leak conductance …

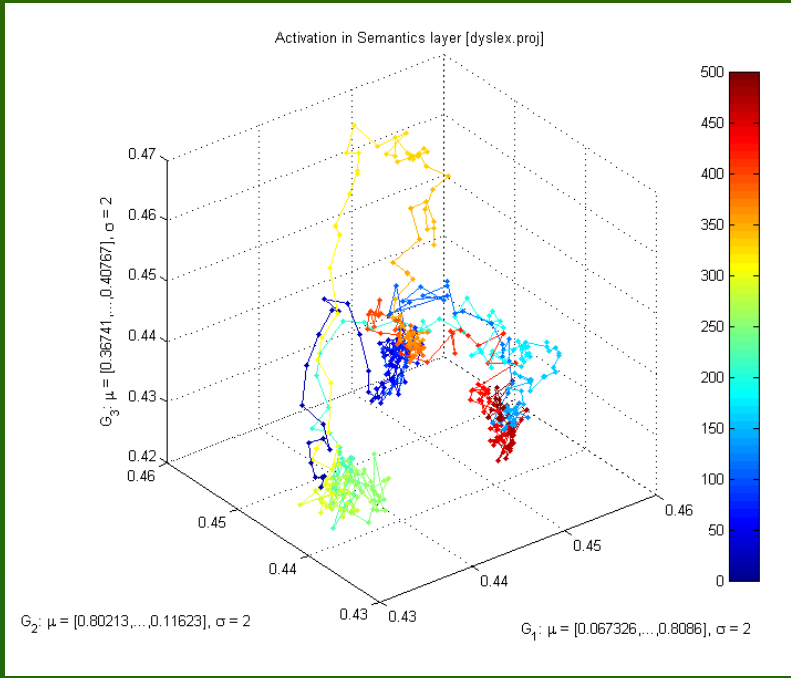
Input activations: transients => basins of attractors => object recognition

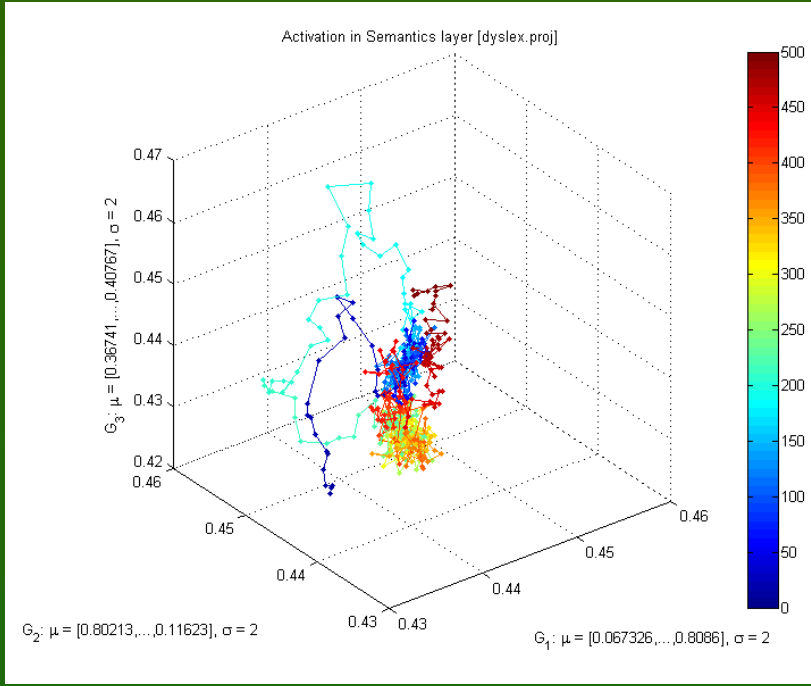
- Normal case: relatively large basins, generalization, average dwell time, moving to other basin of attraction, exploring the activation space.
- Without accommodation (inactive outward rectifying ion channels): deep, narrow basins, hard to move out of the basin, associations are weak.

Accommodation: basins of attractors shrink and vanish because neurons desynchronize due to the neural fatigue. This allows other neurons to synchronize on new stimuli, guided by Spat => V2 => V1 feedback.

This leads to sudden spontaneous weakly related chains of thoughts.

Normal-Autism



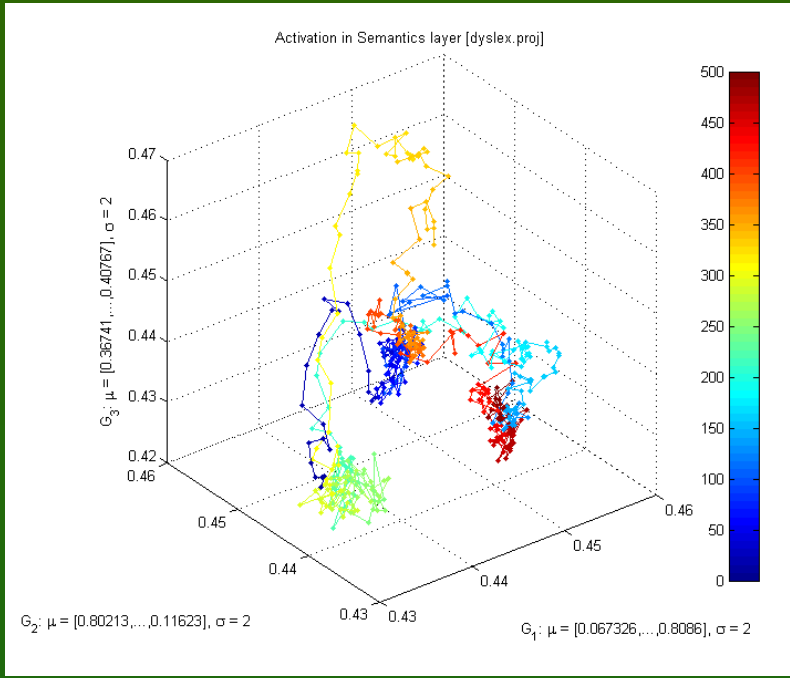


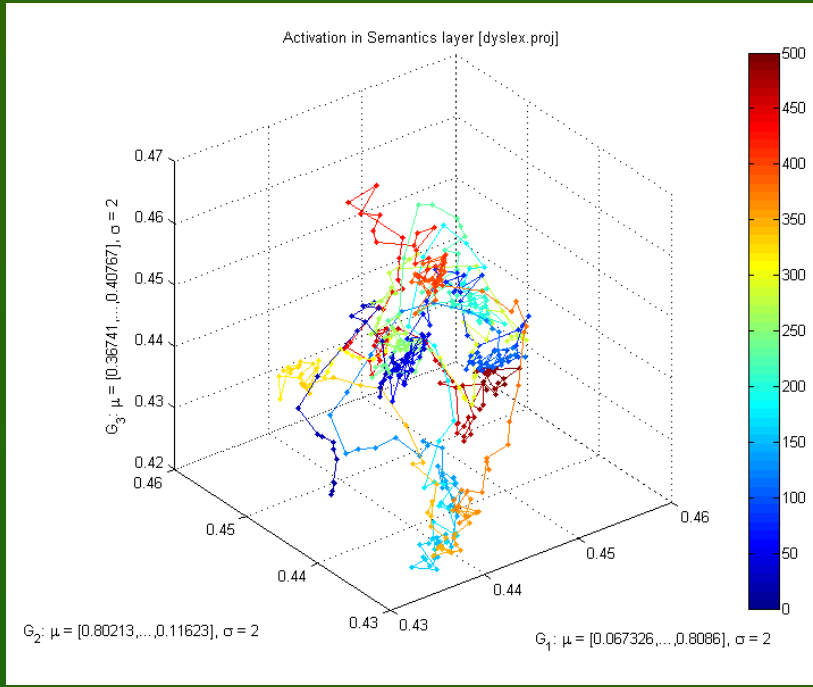
All plots for the flag word, different values of b_inc_dt parameter in the accommodation mechanism. b_inc_dt = 0.01 & b_inc_dt = 0.005

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



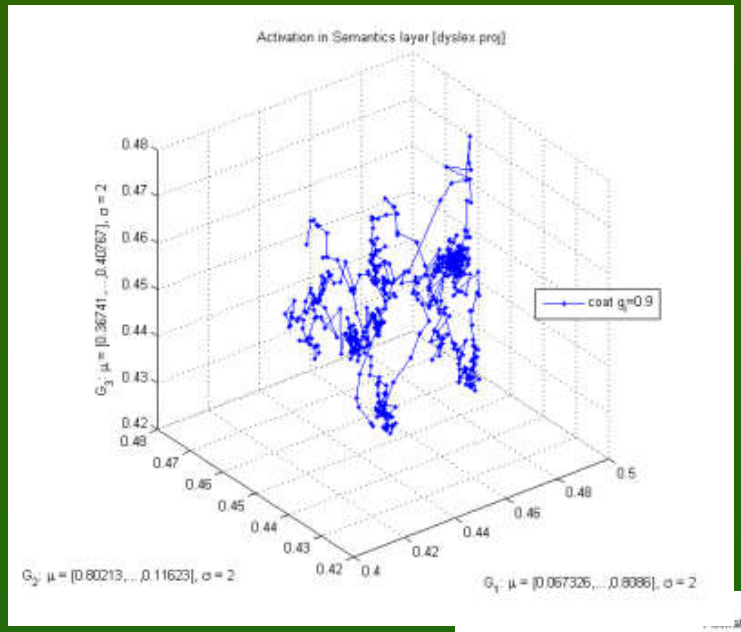


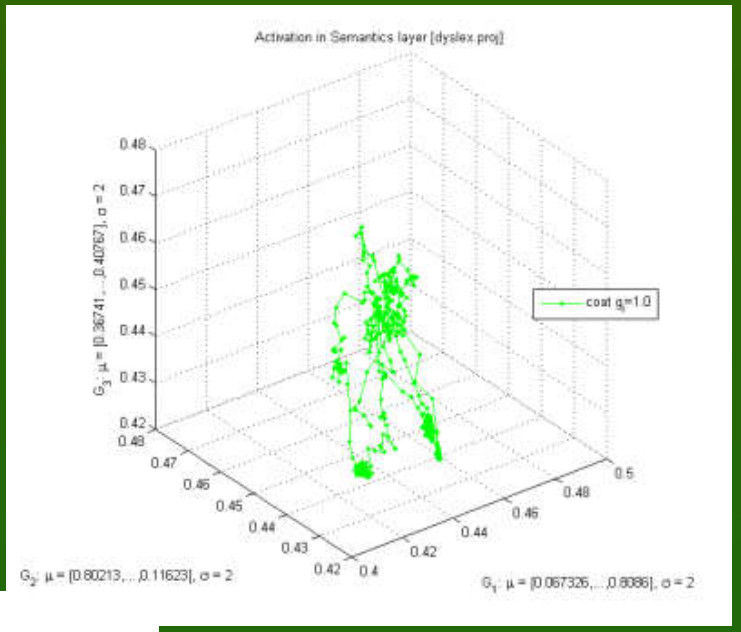
All plots for the flag word, different values of b_inc_dt parameter in the accommodation mechanism. b_inc_dt = 0.01 & b_inc_dt = 0.02

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

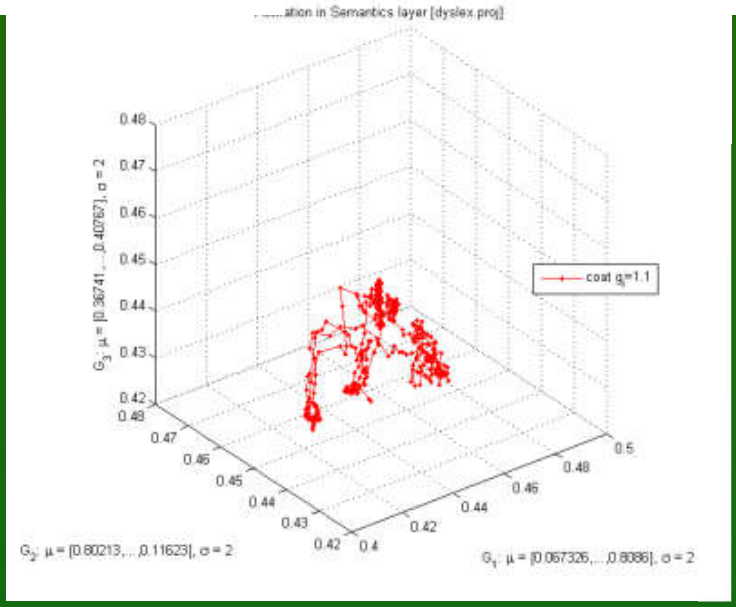
http://kdobosz.wikidot.com/dyslexia-accommodation-parameters

Inhibition





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



Strong inhibition, empty head …

Slower processing due to deep attractors

Hypothesis: deep attractors => longer trapping times => slower processing => fewer 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

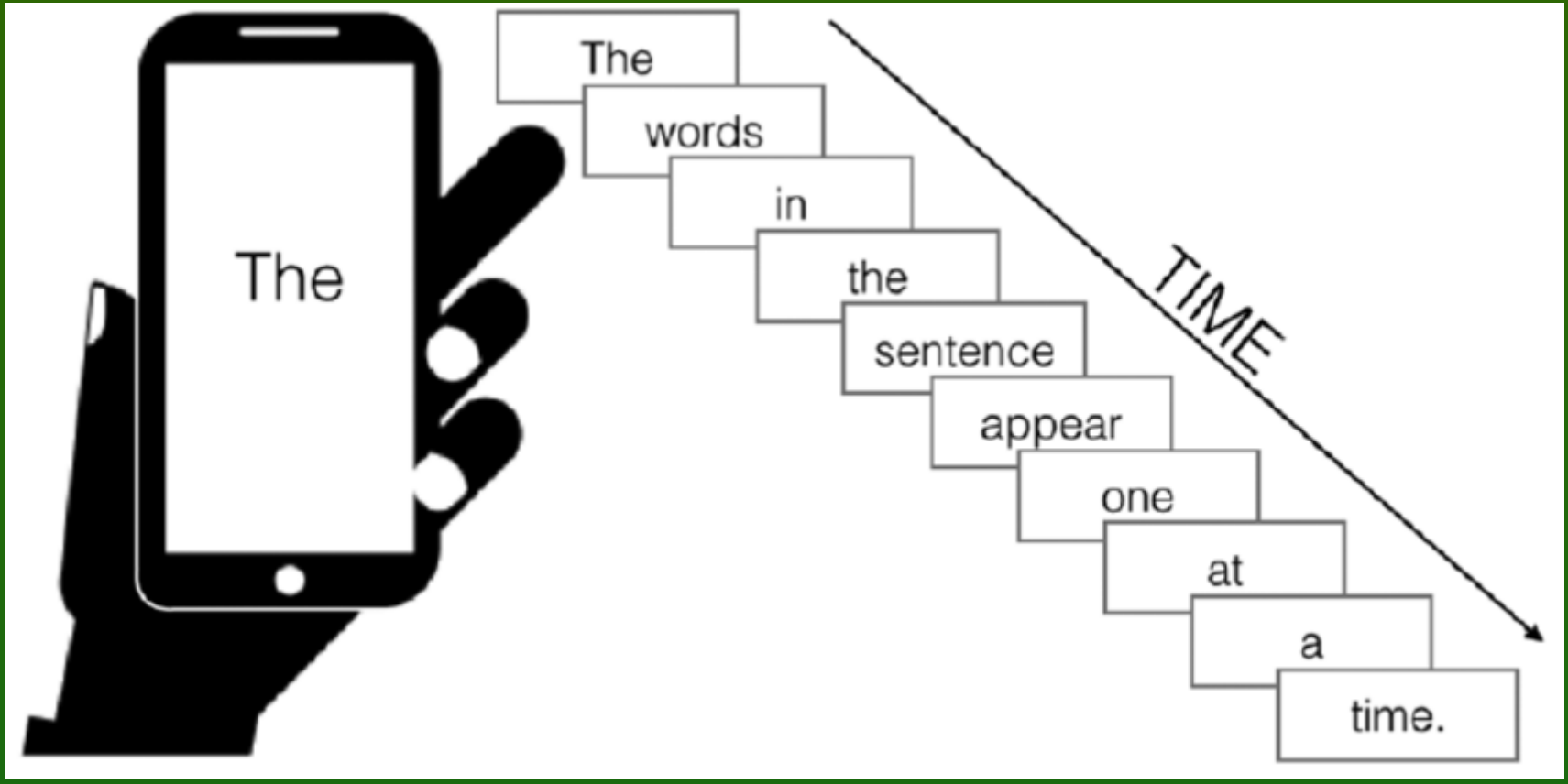
Haigh et al. (2018). Processing Speed is Impaired in Adults with Autism Spectrum Disorder, and Relates to Social Communication Abilities. *Journal of Autism and Developmental Disorders* 48: 2653 (2018).
"Interventions that improve processing speed might improve social communication abilities in ASD".

Good measure of brain processing speeds? Psychometric:

- 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.

Physiological: resynchronization time – microstate duration and transitions.

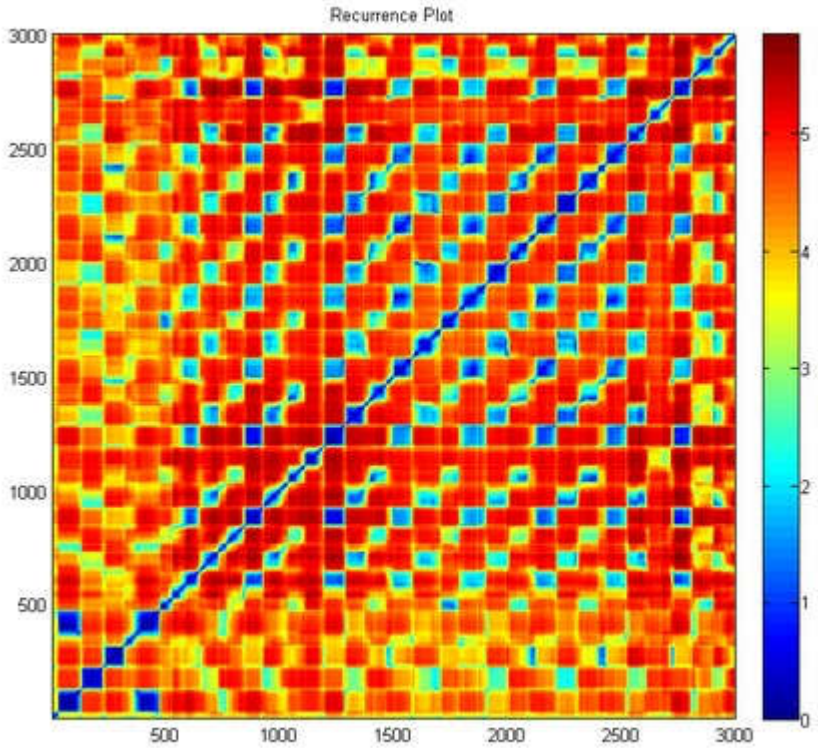
Rapid Serial Visual Presentation

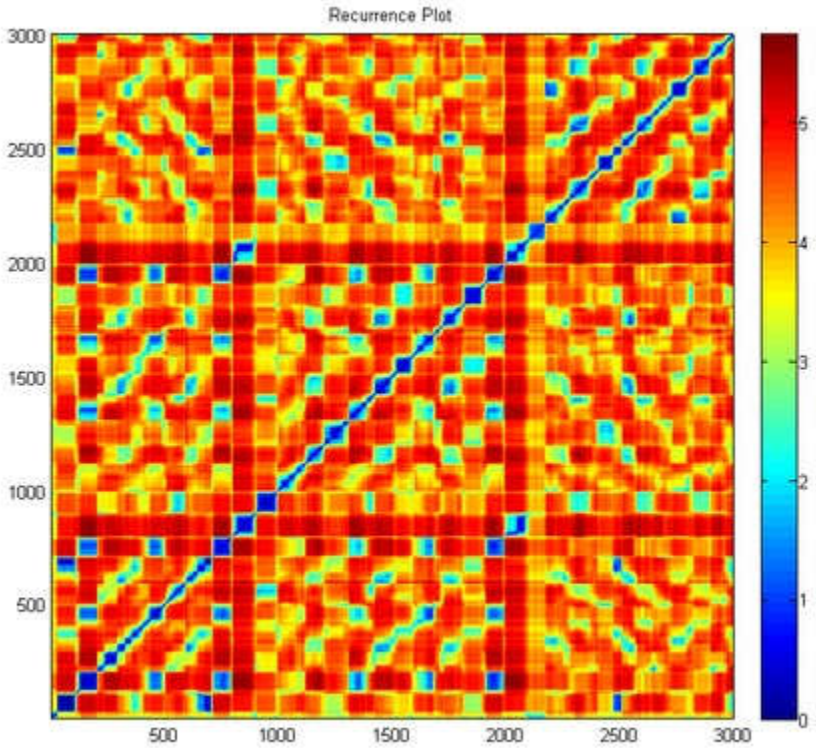


Any RSVP applications for fast reading.

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

RSVP simulations: normal



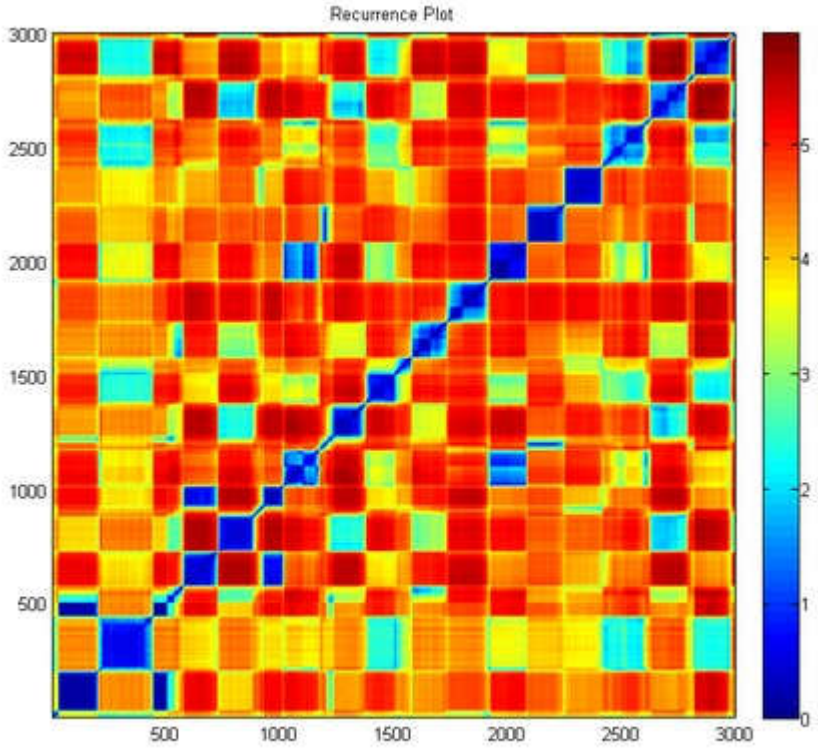


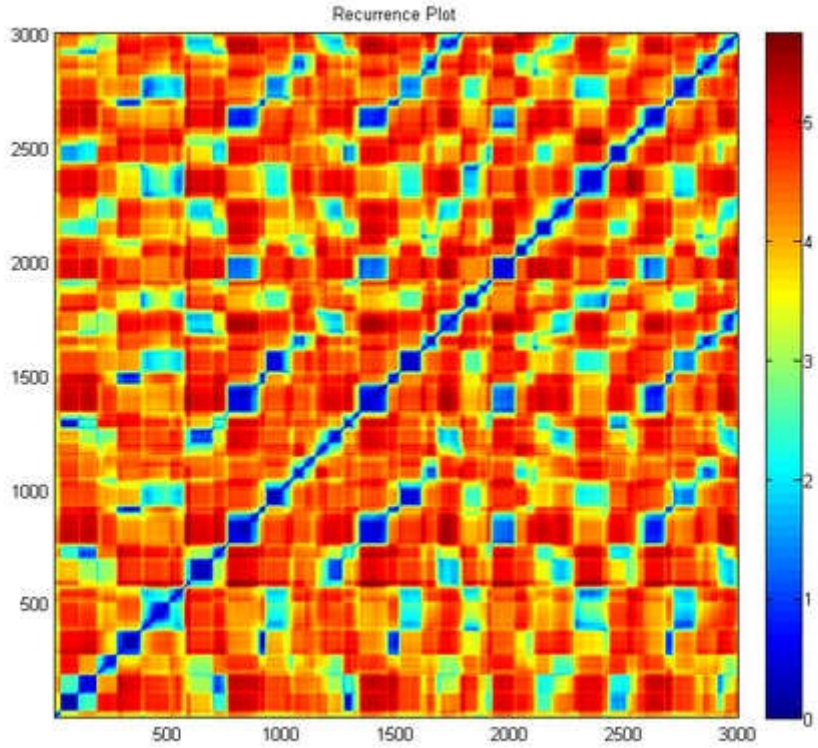
Typical case

normal presentation
associations as dark bands

5x faster presentation
associations disappeared.

RSVP simulations: HFA



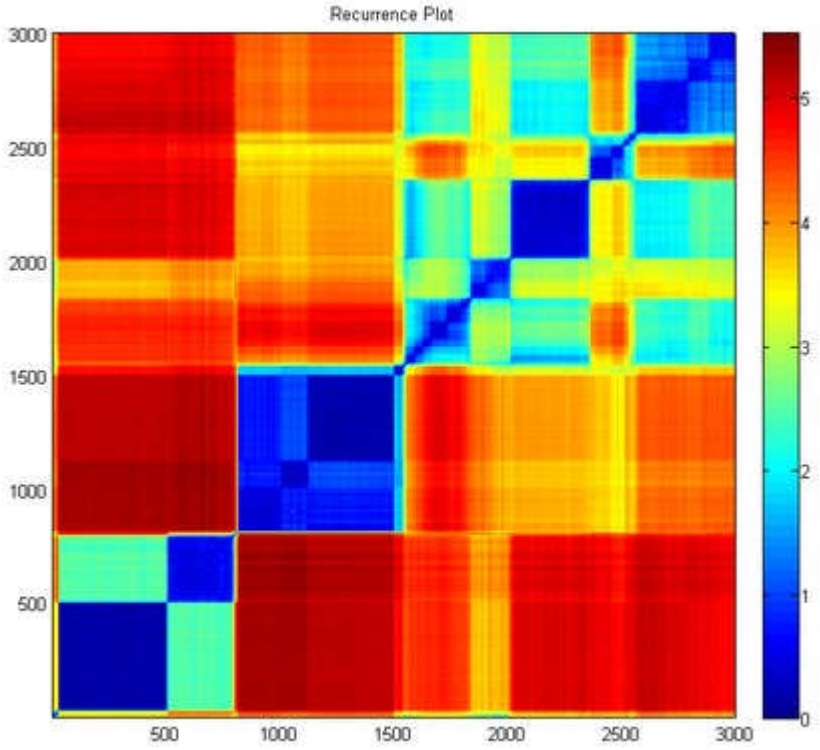


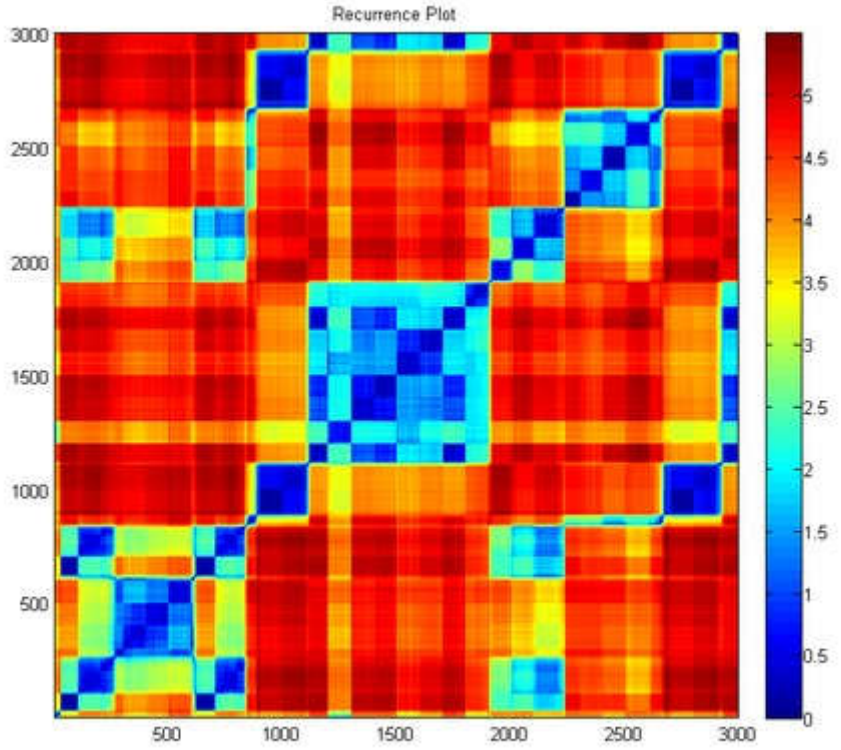
High functioning ASD case (HFA):

normal presentation
long dwelling times

fast presentation
enforced quick resynchronization
more internal stimuli.

RSVP simulations: ASD





normal presentation

Severe ASD case

fast presentation enforces changes
more internal stimulations, but novel states

Behavioral consequences

Deep, localized attractors are formed; what are the consequences?

- Problems with disengagement of attention;
- hyperspecific memory for images, words, numbers, facts, movements;
- strong focus on single stimulus, absorption, easy sensory overstimulation;
- gaze focused on static stimuli, not changing faces, social contact is difficult;
- play with other children is avoided in favor of simple toys;
- play is schematic, fast changes are not noticed (stable states cannot arise);
- echolalia, repeating words without understanding (no associations); nouns are acquired more readily than abstract words like verbs;
- generalization and associations are quite poor; integration of different modalities that requires synchronization is impaired, underconnectivity;
- normal development of the theory of mind is impaired.

Simple basic deficit => host of problems, many insights from such mechanisms.

Great diversity of symptoms <= type/severity of neural properties.

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."

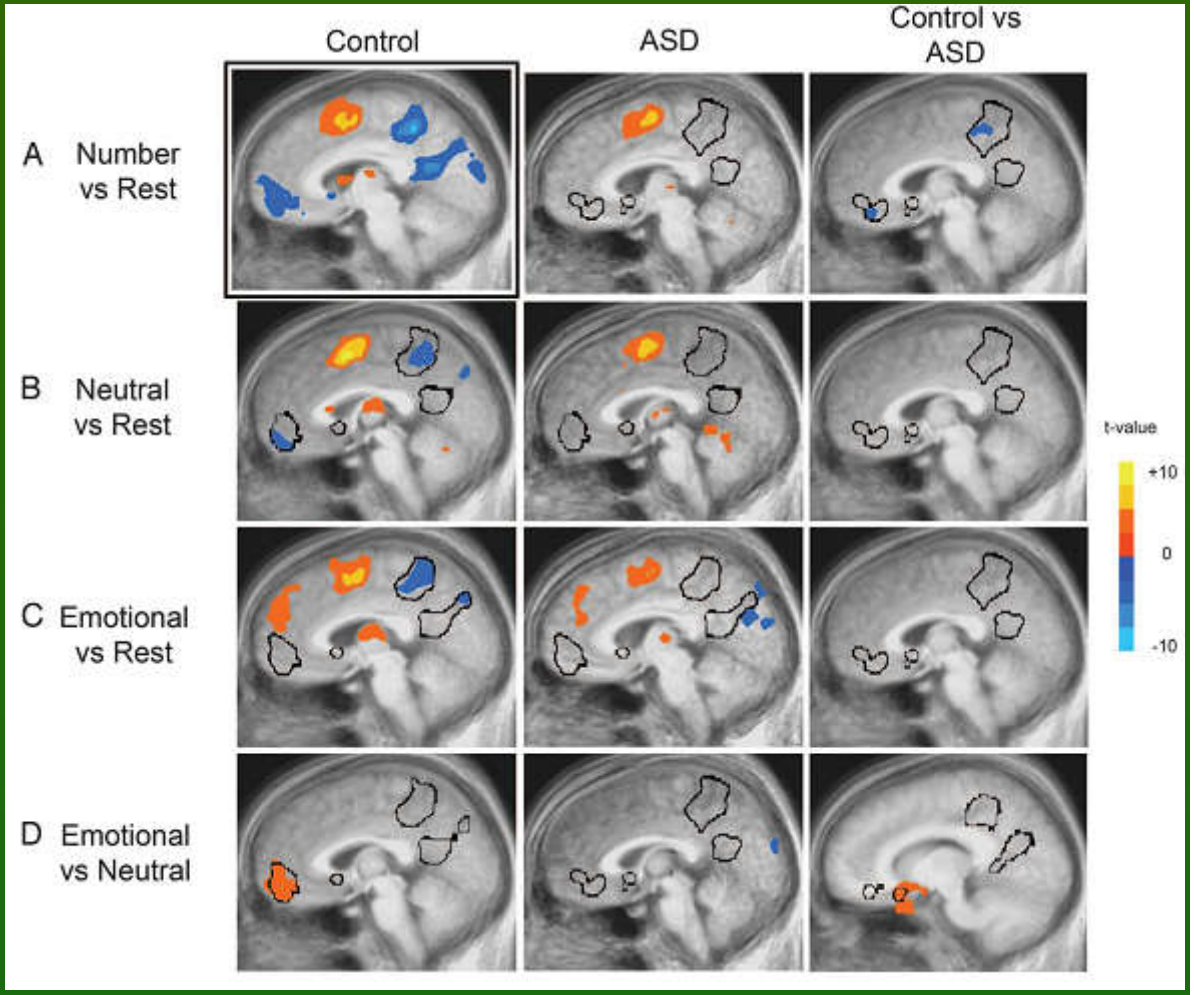
Several newer studies: Mayada Elsabbagh.

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

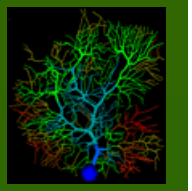
What type of problems with neurons create these types of effects?

- 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).

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.

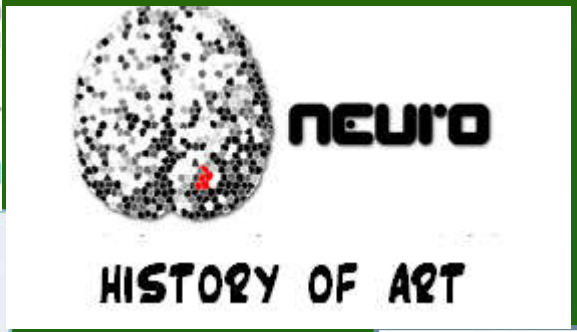
- Is there evidence against deep attractor hypothesis?
- Will more detailed neural models confirm our conclusions?
- How to measure and/or visualize attractors/microstates?
- How does depth/size of basins of attractors depend on these parameters?
- How do attractors depend on neural dynamical properties? Noise? Inhibition strength, local excitations, accommodation, long-distance synchronization?
- 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?

Soul or brain: what makes us human? Interdisciplinary Workshop with theologians, Toruń 19-21.10.2016

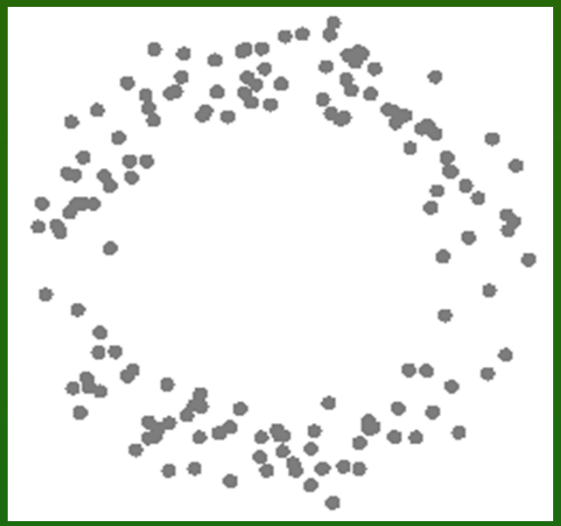
Monthly international developmental seminars (2017): Infants, learning, and cognitive development

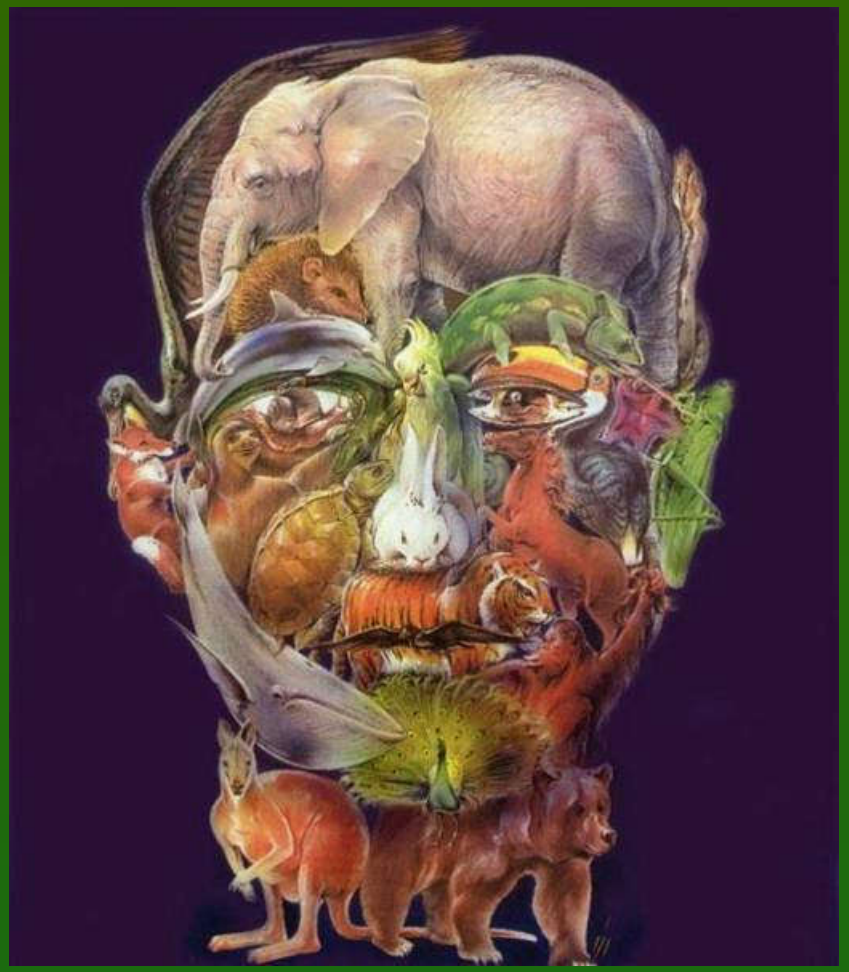
Disorders of consciousness 17-21.09.2017

Autism: science, therapies 23.05.2017



Thank you for synchronizing your neurons!





Google: W. Duch

=> papers, talks, lecture notes …