Neuropsychiatric phenomics: understanding mental disease using computational simulations
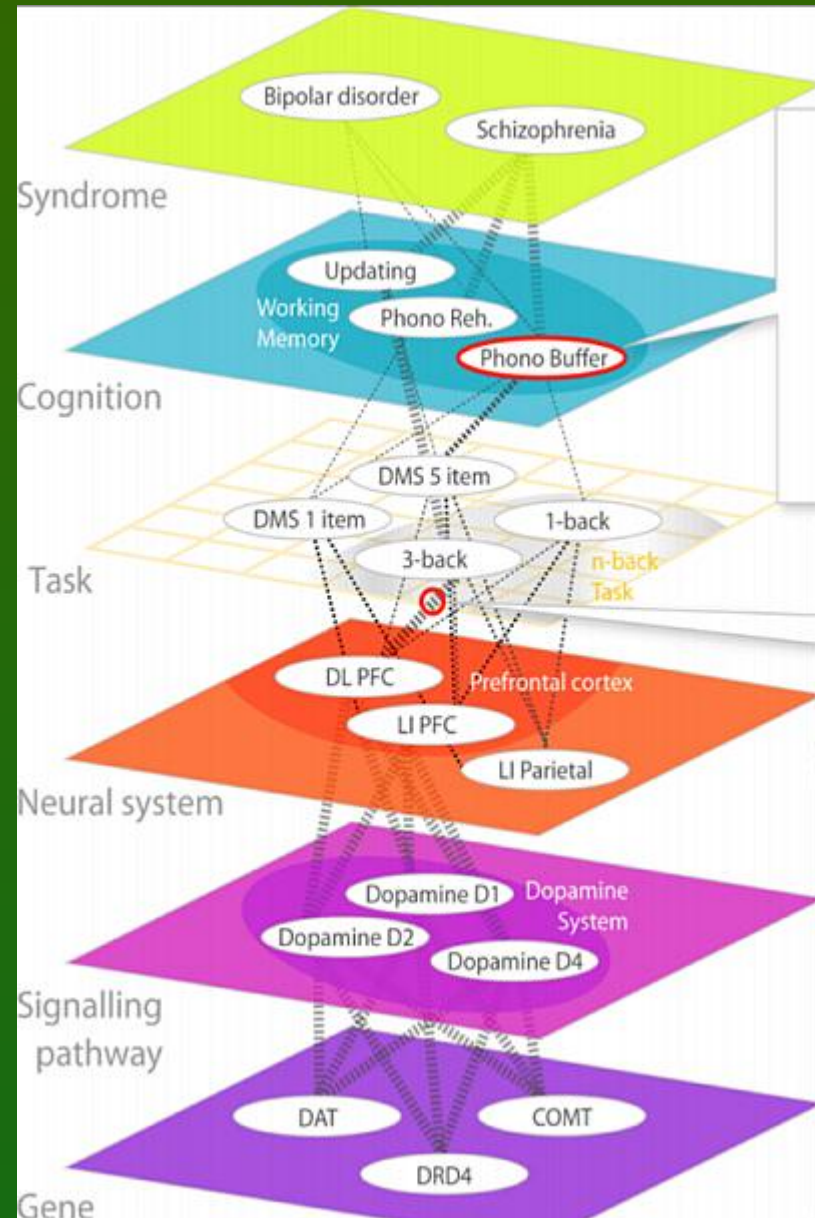
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Neuropsychiatric Phenomics Levels

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

Strategy for Phenomics Research

The Consortium for Neuropsychiatric Phenomics: bridge all levels, one at a time, from environment to syndromes.

Neural systems are in the central position.
Our strategy: identify biophysical parameters of neurons required for normal neural network functions and leading to abnormal cognitive phenotypes, symptoms and syndromes.

- Start from simple neurons and networks, increase complexity.

- Create models of cognitive function that may reflect some of the symptoms of the disease, for example problems with attention.

- Test and calibrate the stability of these models in a normal mode.

- Determine model parameter ranges that lead to similar symptoms.

- Relate these parameters to the biophysical properties of neurons.

Example: ASD/ADHD relation to calcium regulation.

Theories, theories


Best book on ASD so far:

- Zimmerman Andrew W. (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).

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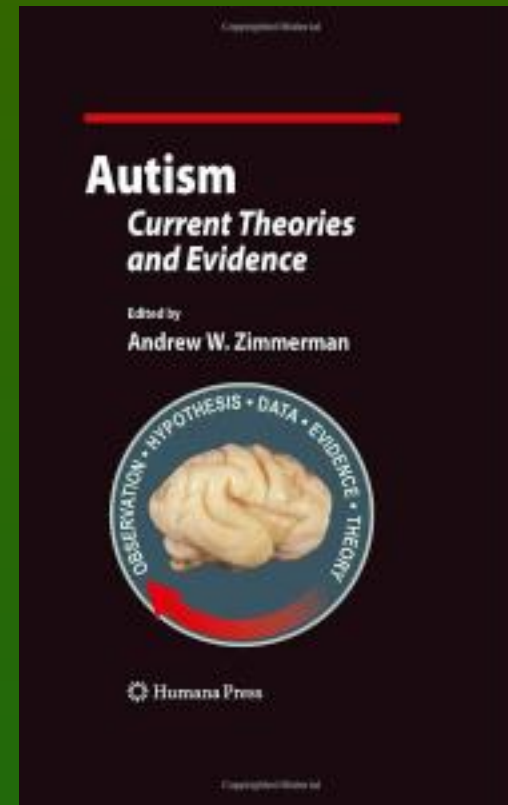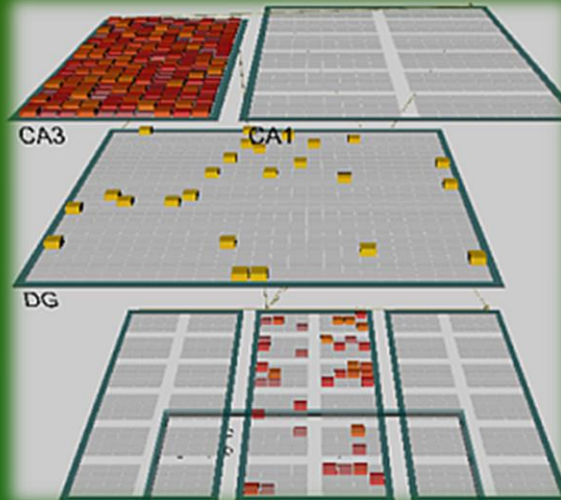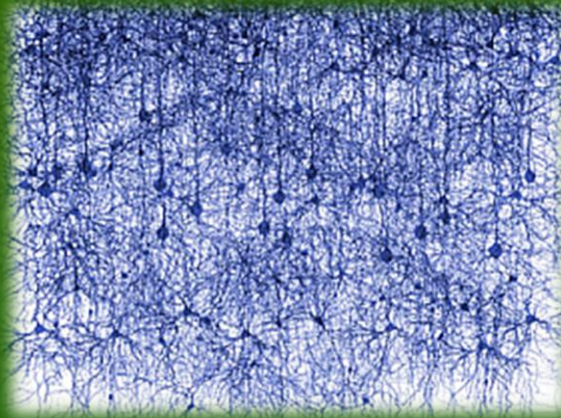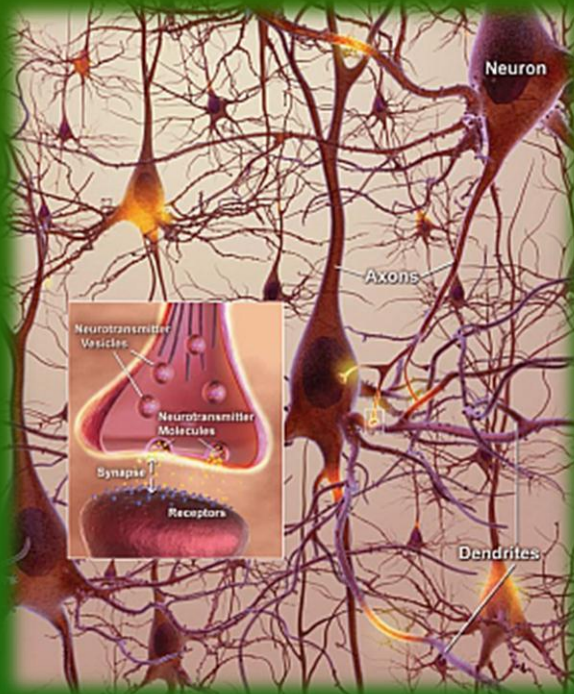
From Genes to Neurons
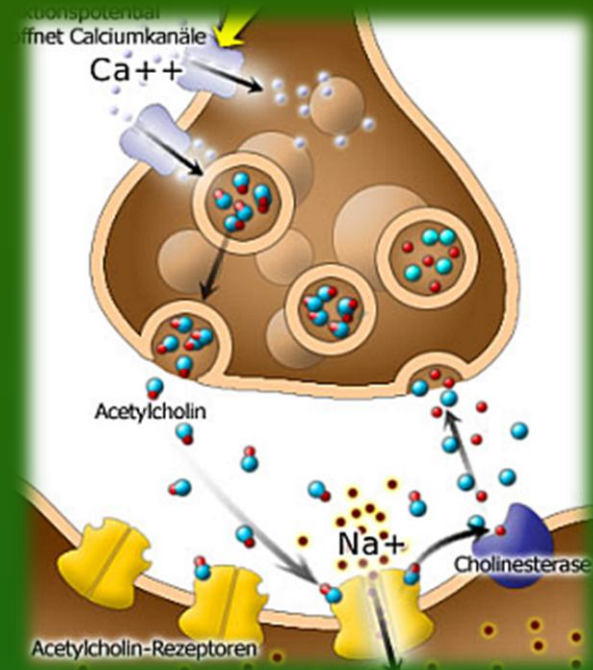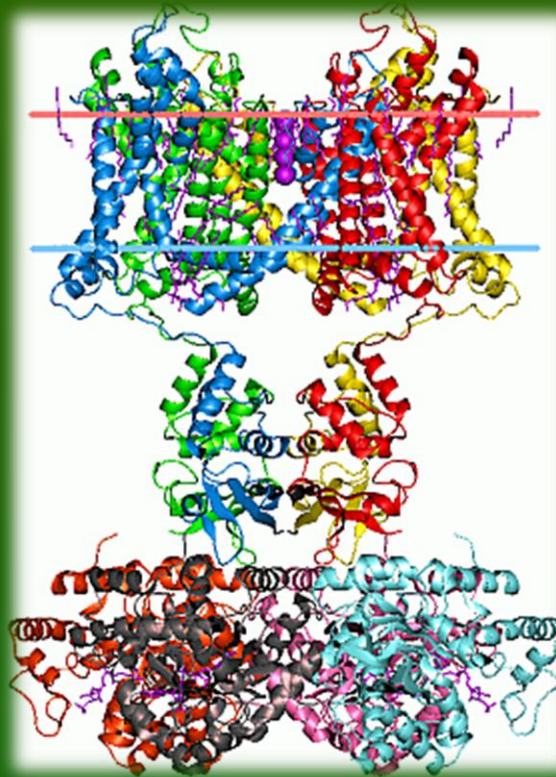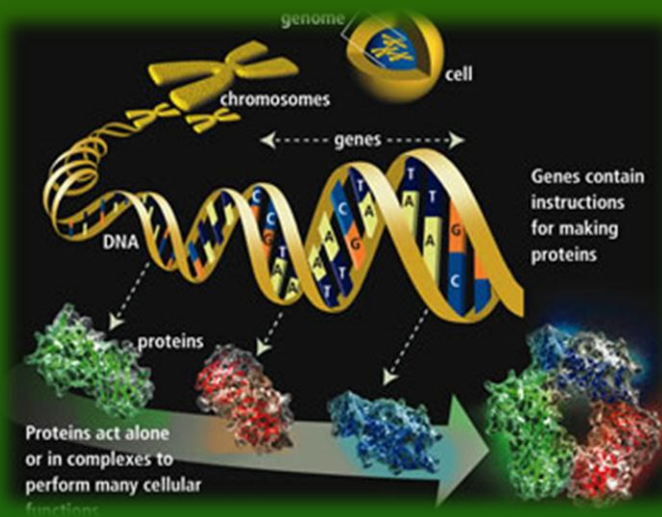
Genes => Proteins => receptors, ion channels, synapses
=> neuron properties, networks, neurodynamics
=> cognitive phenotypes, abnormal behavior, syndromes.

# From Neurons to Behavior

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

Genes & functions

http://www.sciencebasedmedicine.org/?p=5662
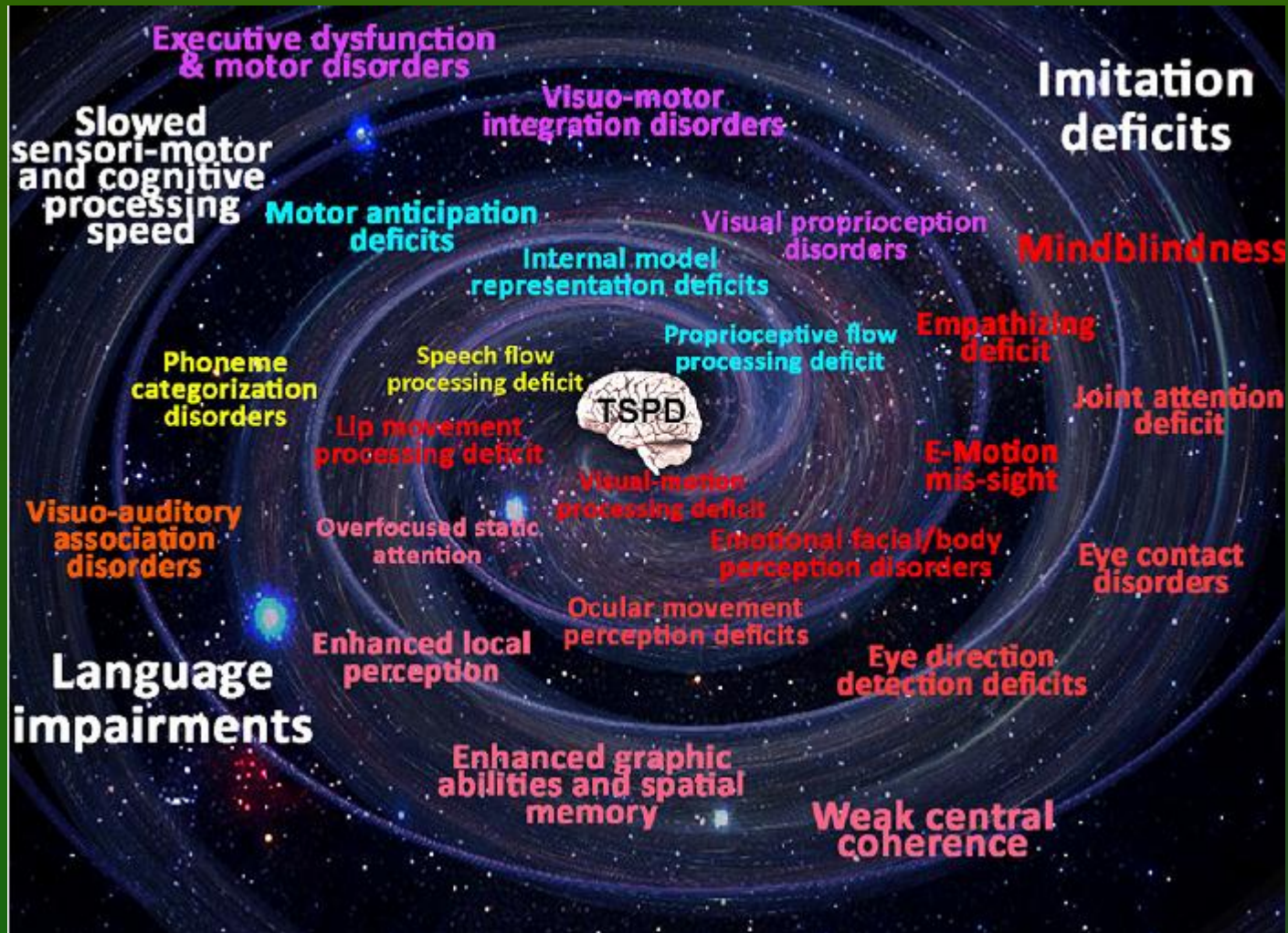
Pinto, D. + 180 coauthors ... (2010). Functional impact of global rare copy number variation in autism spectrum disorders Nature DOI: 10.1038/nature09146
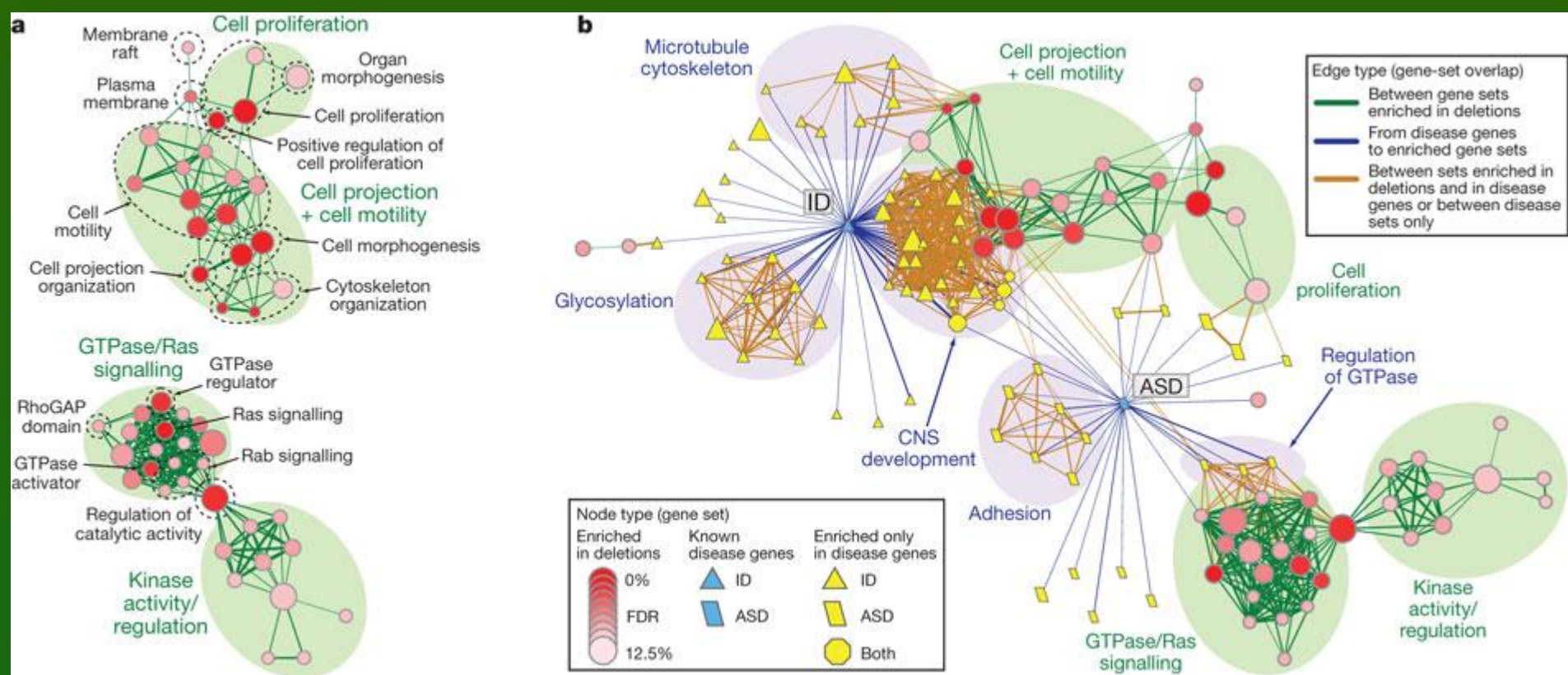
Temporo-spatial processing disorders

B. Gepner, F. Feron, Autism: A world changing too fast for a mis-wired brain? Neurosci. Biobehav. Rev. (2009).

Models

Models at various level of detail.

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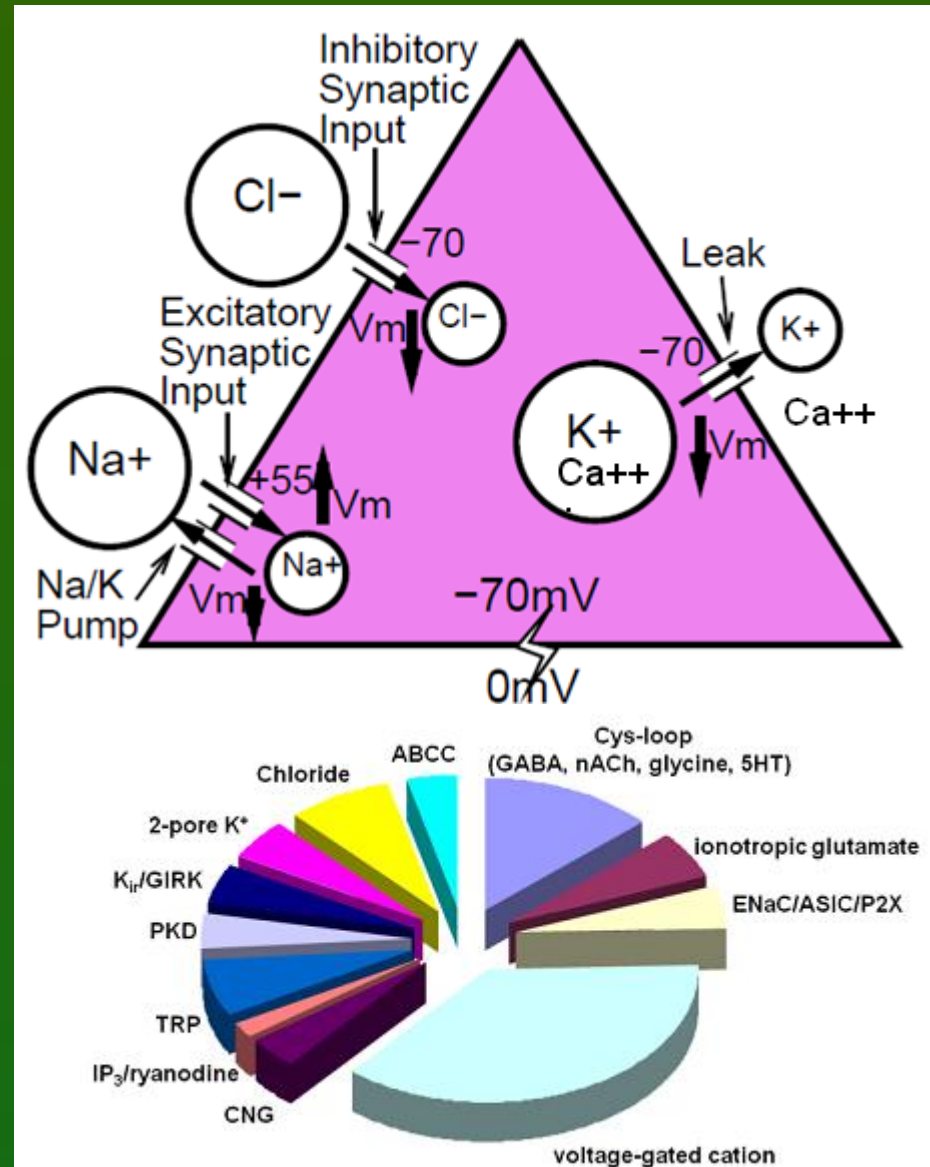
Models of attention:

- Posner spatial attention (see Alex Gravier et al. poster);

- attention shift between visual objects.

Models of word associations:

- sequence of spontaneous thoughts.

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.

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).

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.

ADHD: fast transitions
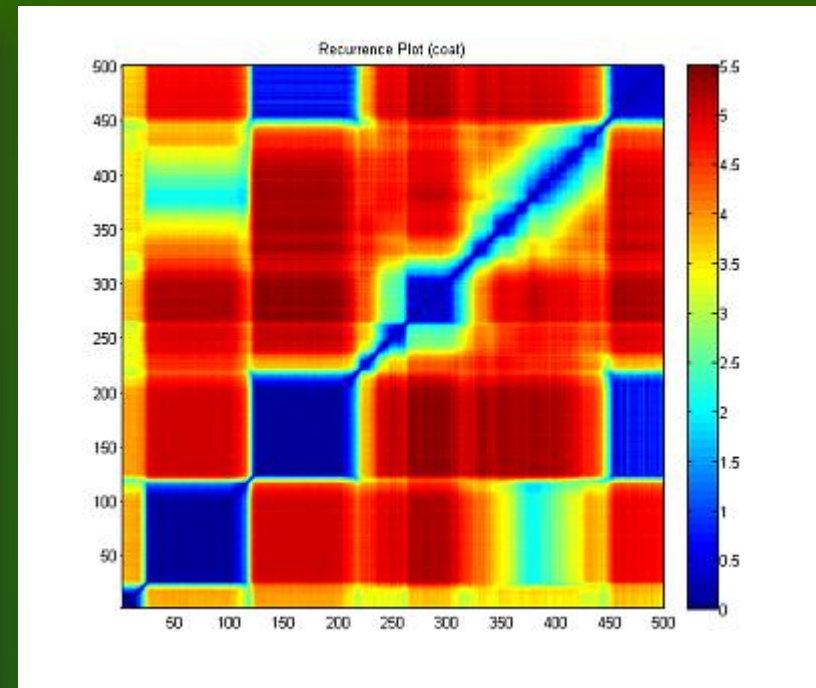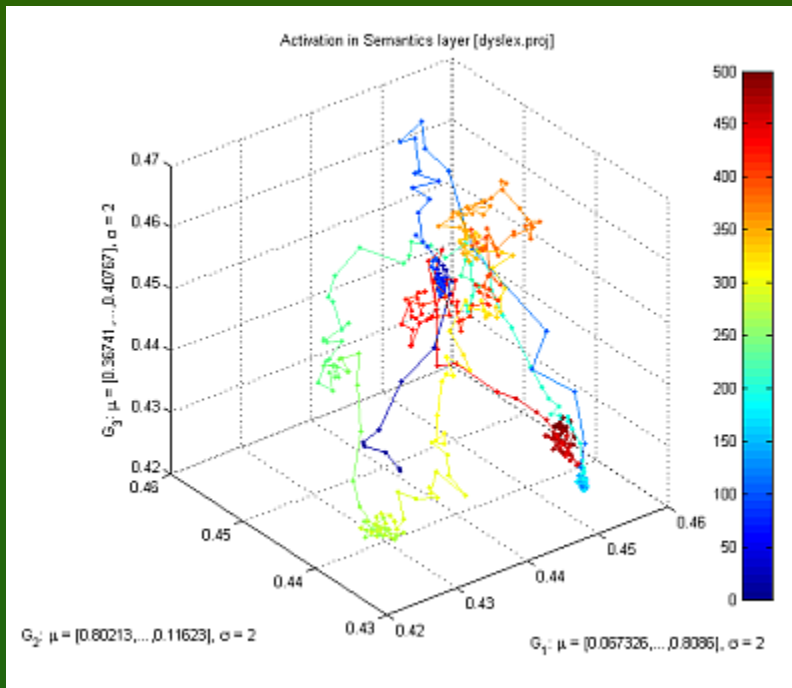
Attention is focused only for a brief time and than moved to the next attractor basin, some basins are visited for such a short time that no action may follow, generating the feeling of confusion, not being conscious of fleeting thoughts, as seen in the recurrence plots or by the long jumps between attractors.

Normal-Autism
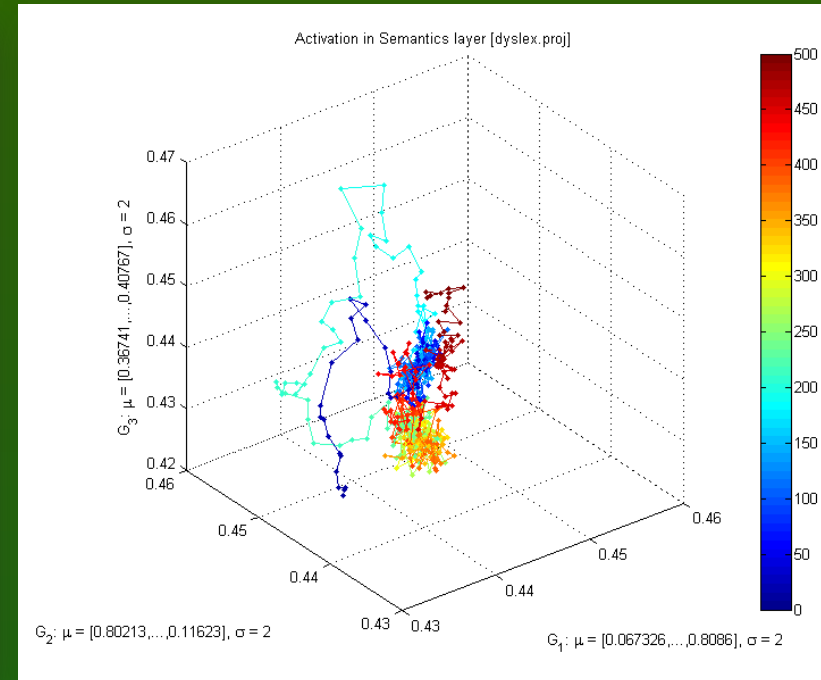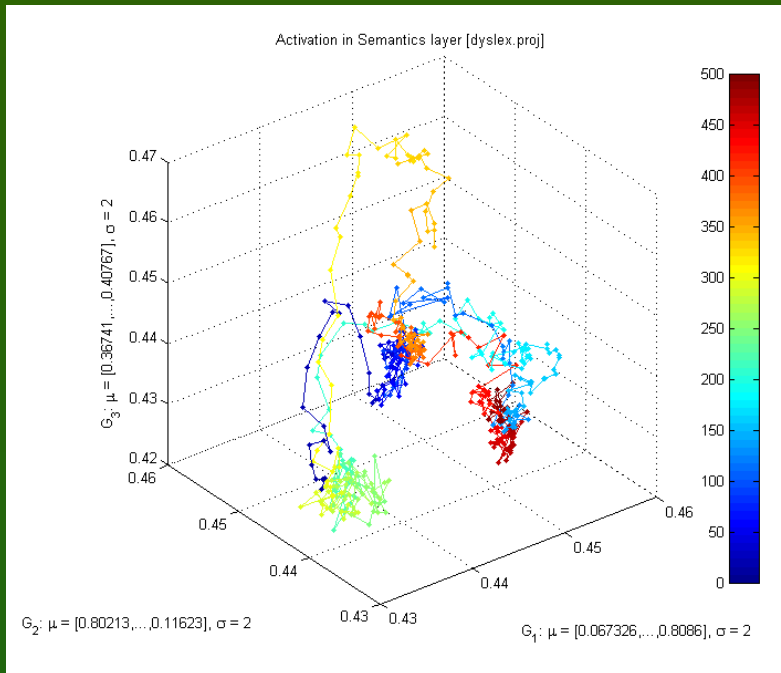
Semantic layer trajectory following prompt by the *flag* written word.

Left b_inc_dt = 0.01, right b_inc_dt = 0.005 (low accomodation)
Neurons synchronize too strongly, creating deep (strong) attractors,
decreasing the flexibility of changing brain states.

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

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 simple stimuli, not faces, contact is difficult;
- echolalia, repeating words without understanding (no associations); nouns are acquired more readily than abstract words like verbs;
- play is schematic, fast changes are not noticed (stable states cannot arise);
- play with other children is avoided in favor of simple toys;
- generalization and associations are quite poor; integration of different modalities that requires synchronization is impaired, connections are weak;
- abnormal development – theory of mind, mirror system is impaired.

Simple basic deficit => host of problems, insights from simple mechanism.
Expect great diversity, depending on local expression and severity.

Research/diagnostic consequences

Many problems at genetic/molecular level may lead to the same behavioral symptoms => problems for statistically-oriented research methods.

- Inconclusive results on diet: several studies show some improvement, other studies show no effect, perhaps due to diversity.
- Genetic mutation should give very weak signals: in a given population of autistic patients only small fraction will have a given mutation.
- Pharmacological and other treatments will have limited success.
- Need for a better diagnostics at molecular/genetic level!

Strategy: behavior ⇔ neural properties ⇔ molecular level;
- find neural parameters that affect behavior in a specific way;
- try to relate them to molecular properties in synapses, various receptors, ion channels (pore forming proteins), membrane properties;
- try to find markers for specific abnormalities.
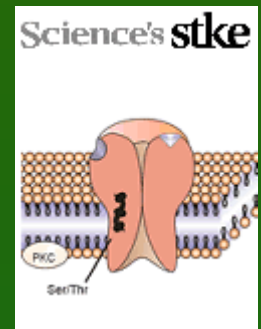
Mistaking symptoms for causes

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

Brains & Music 22-24.05.2011!
http://www.kognitywistyka.umk.pl/2011/