Diagnosis based on nonlinear analysis of brain neurodynamics

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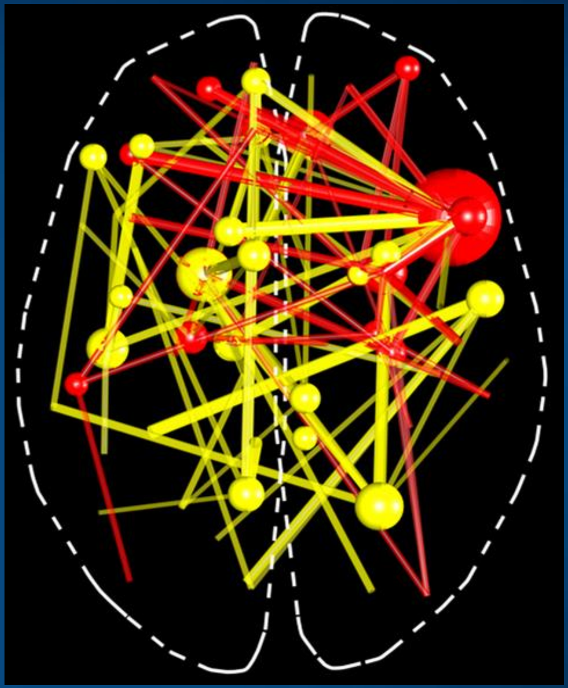
161st IBIB Seminar: Computer-aided diagnosis support by digital pathology 11/2018

Plan

- Global and Emerging Brain Initiatives: large scale brain research collaborations.
- Machine Learning, tensor decompositions and importance of features.
- Brain connectivity for psychiatric diagnosis.
- Brain fingerprints and neurodynamics.
- Perspectives.



Global Brain Initiatives

Costs of brain diseases

European Brain Council (EBC) reports (2010; 2014).

Gustavsson et al. (2011). Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(10), 718–779.

Brain disease ≈ 45% of the total annual health budget of Europe!

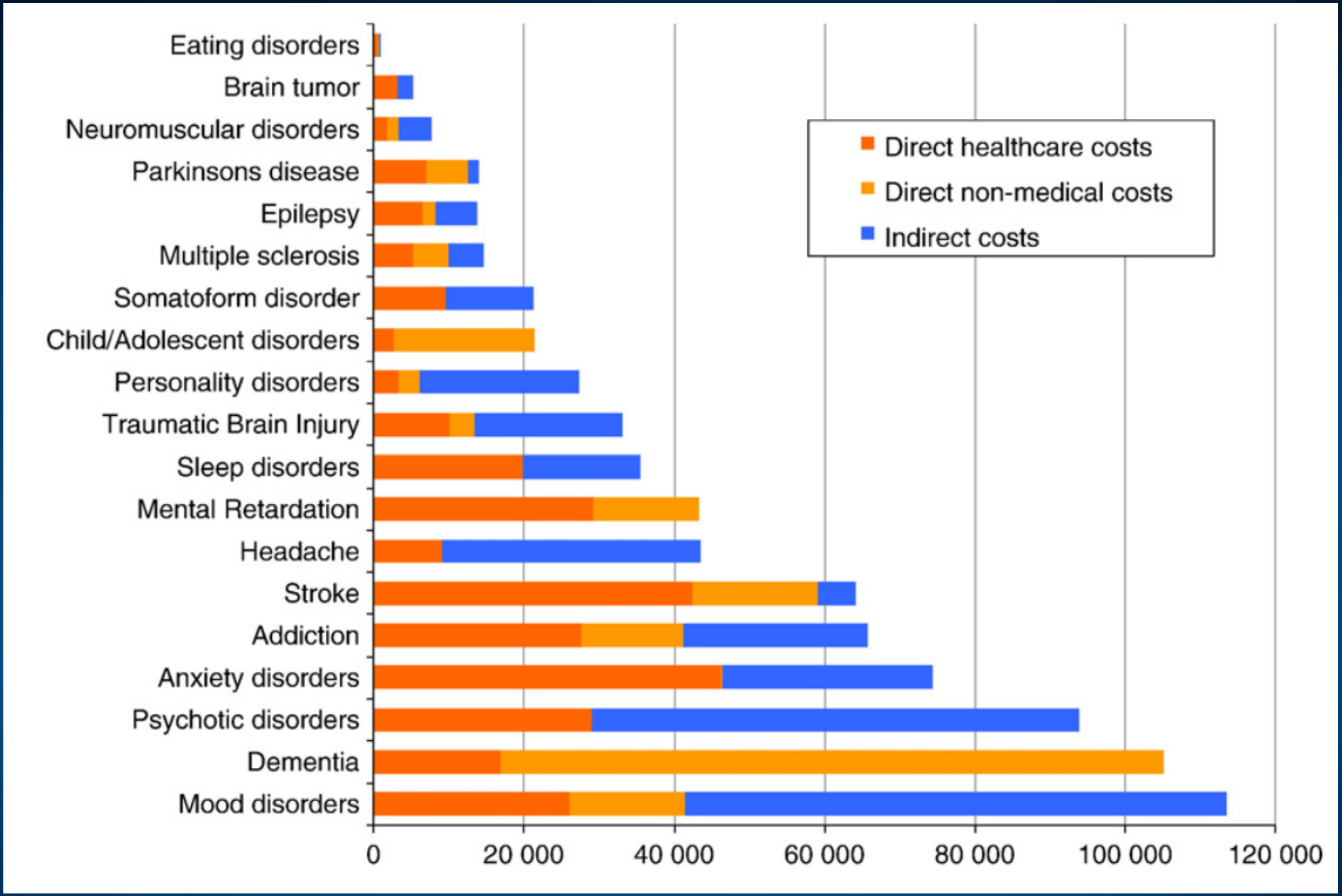
Total cost of brain disorders in EU estimated in 2010:
798 billion €/year, average direct health care costs represent 37%, direct nonmedical costs 23%, and indirect costs 40%.

1/3 of all European citizens, or about 179 million, had at least one brain disorder during their lifetime.

China: >20% of population (~250 mln) suffering from some mental disorder.

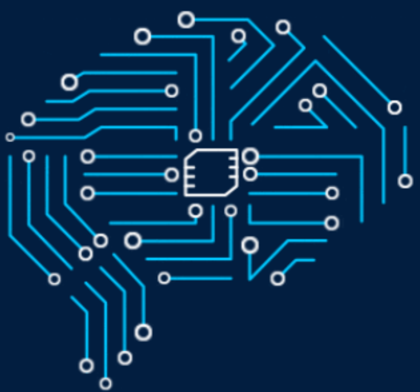
Total costs of disorders of the brain in Poland, 2010 estimates.

Addiction	Anxiety	Dementia	Epilepsy	Headache	Mood	Psychotic	Stroke	x1000
1 201	5 261	358	298	12 025	2 499	371	503	# people
2 501	2 882	2 480	745	1 559	4 489	3 723	2 187	mln €



Total cost by disorder and type of cost (€PPP million, 2010), all disorders.
Gustavsson et al. *European Neuropsychopharmacology* 2011.
In most cases there are no methods for objective clinical diagnosis!

BRAIN INITIATIVE



Advance Neurotechnologies

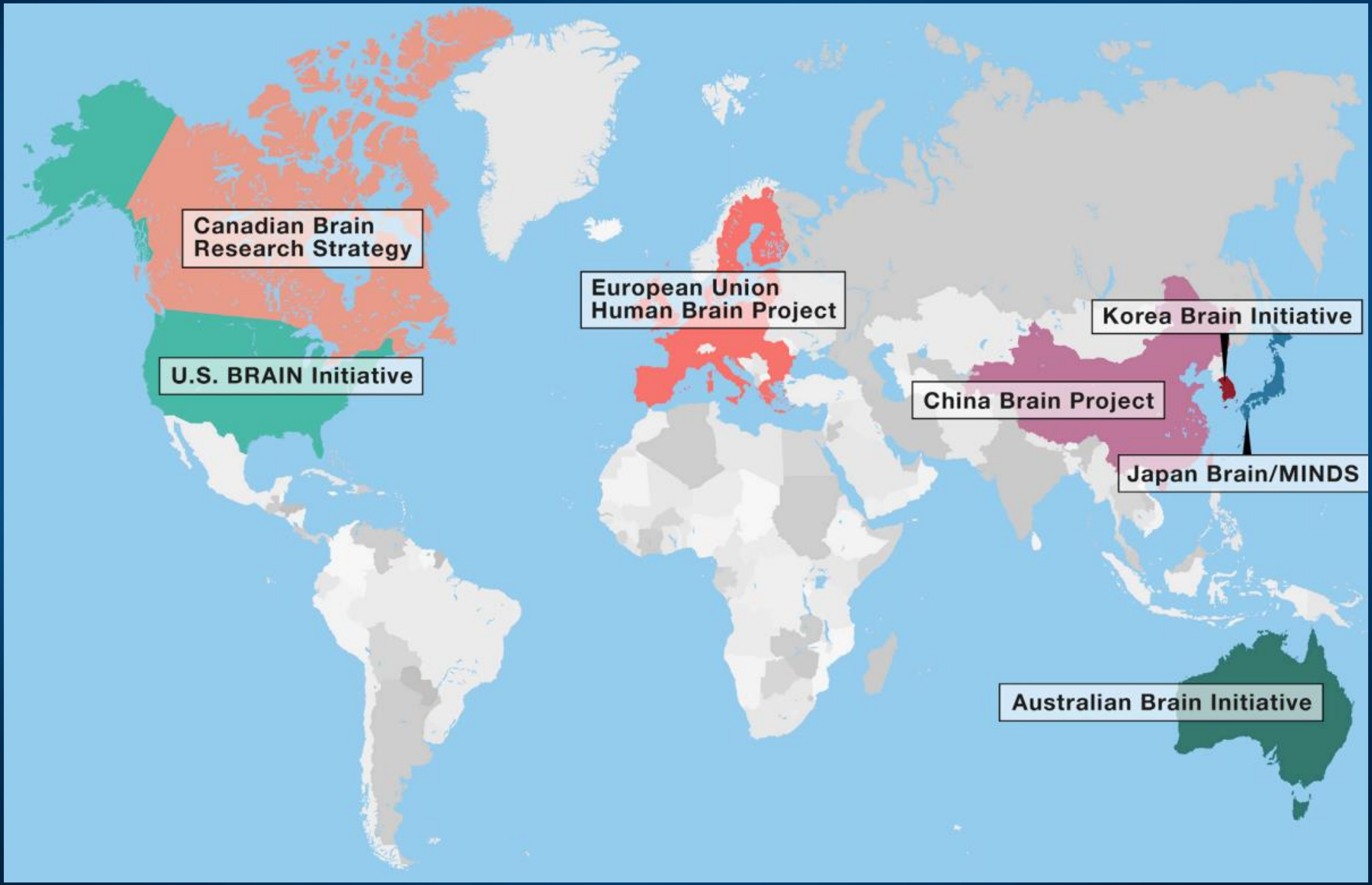
Accelerate the development and application of new neurotechnologies.

Support multi-disciplinary teams and stimulate research to rapidly enhance current neuroscience technologies and catalyze innovative scientific breakthroughs.

Human Brain Project, EU Flagship, and Obama BRAIN Initiative (2013):
Brain **R**esearch through **A**dvancing **I**nnovative **N**eurotechnologies.

"Develop new technologies to explore how the brain's cells and circuits interact at the speed of thought, ultimately uncovering the complex links between brain function and behavior. Explore how the brain records, processes, uses, stores, and retrieves vast quantities of information. Help bring safe and effective products to patients and consumers."

International Brain Initiatives



The mission of IEEE Brain is to facilitate cross-disciplinary collaboration and coordination to advance research, standardization and development of technologies in neuroscience to help improve the human condition.

20 IEEE Societies are involved, including:

IEEE Computational Intelligence Society; Computer Society; Consumer Electronics Society; Digital Senses Initiative; Robotics and Automation Society; Sensors Council; Signal Processing Society; Society on Social Implications of Technology; **Systems, Man, and Cybernetics Society**, International Neuroethics Society, and a few other societies.

Satya Nadella (CEO, Microsoft): to celebrate National Disability Employment Awareness Month, shared examples of how technology can be applied to empower the more than one billion people with disabilities around the world.

Workshop on Brain-Machine Interface Systems
Global Current and Emerging Brain Initiative Meeting
Brain Hackathon

IEEE SMC
Systems, Man, and Cybernetics Society

Part of the Brain-Machines Interface Workshop and SMC2018.

The IEEE SMC Society and the IEEE President, James Jefferies, are proud to invite you on to a special meeting of **Global Current and Emerging Brain Initiative leaders** and representatives from other groups working on large-scale multi-year brain projects from Australia, Canada, China, Europe (HBP), Japan, Korea, New Zealand, **Poland**, Russia, and US (NSF and NIH), with representatives from the **IEEE Brain Initiative**, International Neuroethics Society, industry, and other stakeholders.

IEEE welcomes collaborative discussions with all stakeholders to better align and integrate IEEE with other existing brain efforts.

incf | Neuro Informatics 2019

12th INCF Congress on Neuroinformatics Warsaw 31.08-2.09, 2019.
Neuroimaging, computational neuroscience, artificial intelligence.

International Neuroinformatics Coordination Facility (INCF) goal:
integrate and analyze diverse data across scales, techniques, and species to understand the brain and positively impact the health and well being of society.

Polish INCF Node since 2017 is at the Nicolaus Copernicus University in Toruń.

On the threshold of a dream …

Neuroinformatics final goal: optimize brain processes!

To repair damaged brains and increase efficiency of healthy brains we need precise diagnosis:

1. Find fingerprints of specific activity of brain structures (regions, networks) using neuroimaging technology (and new neurotechnologies).
2. Create models of cognitive architectures that help to understand information processing in the brain.
3. Create new clinical diagnostic tools and therapeutic procedures.
4. Use neurofeedback based on decoding and changes in connectivity and close-loop system that directly stimulate the brain.

G-tec wireless NIRS/EEG.

Machine Learning

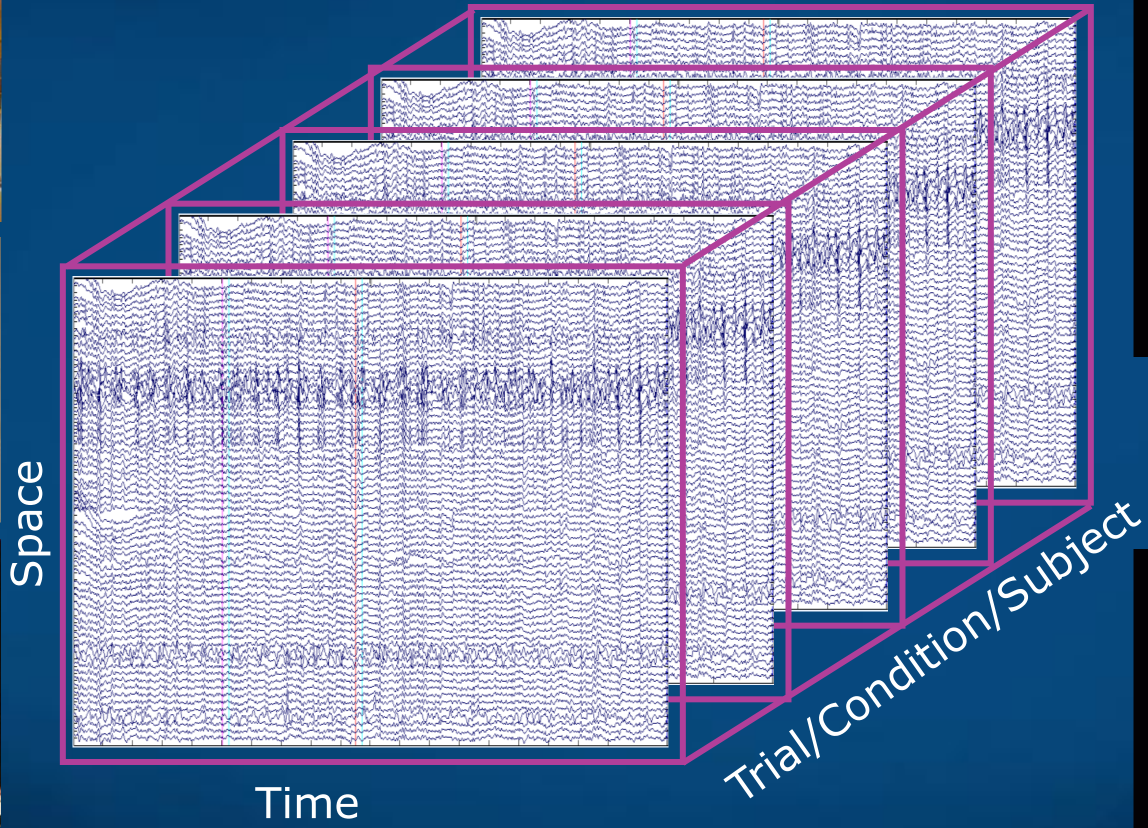
A few important ML developments

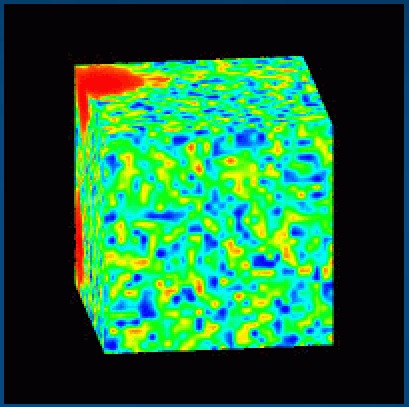
[List of projects]

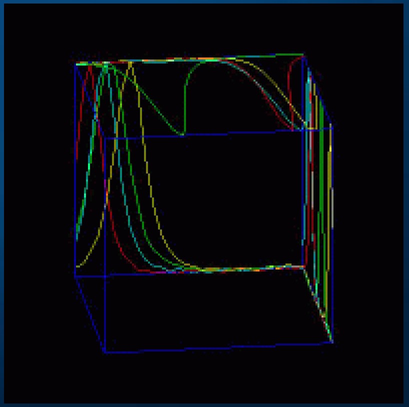
1. Understanding NN functions
   - Visualization of network and error functions
   - Neurofuzzy systems: Feature Space Mapping (FSM)
   - Prototype-rules (P-rules), more general than fuzzy rules
2. NN learning algorithms
   - Support Vector Neural Training (SVNT)
   - Almost Random Projection Method (aRPM)
   - Transformation-based learning, heterogeneous systems
3. Foundations of CI
   - K-representability and problems with complex logic
   - Projection Pursuit Learning, Quality of Projected Clusters (QPC)
   - Support Feature Machines (SFM) and Universal Learning Machines (ULM)
4. Meta-learning by searching in the model space
   - Framework for Similarity-Based Learning
   - Universal Meta-Learning, complexity based

From Two-way to Multi-way Analysis
Integration and Fusion of Various Modalites
EEG + fNIRS + fMRI

A. Cichocki Lab
RIKEN Brain Science Inst.

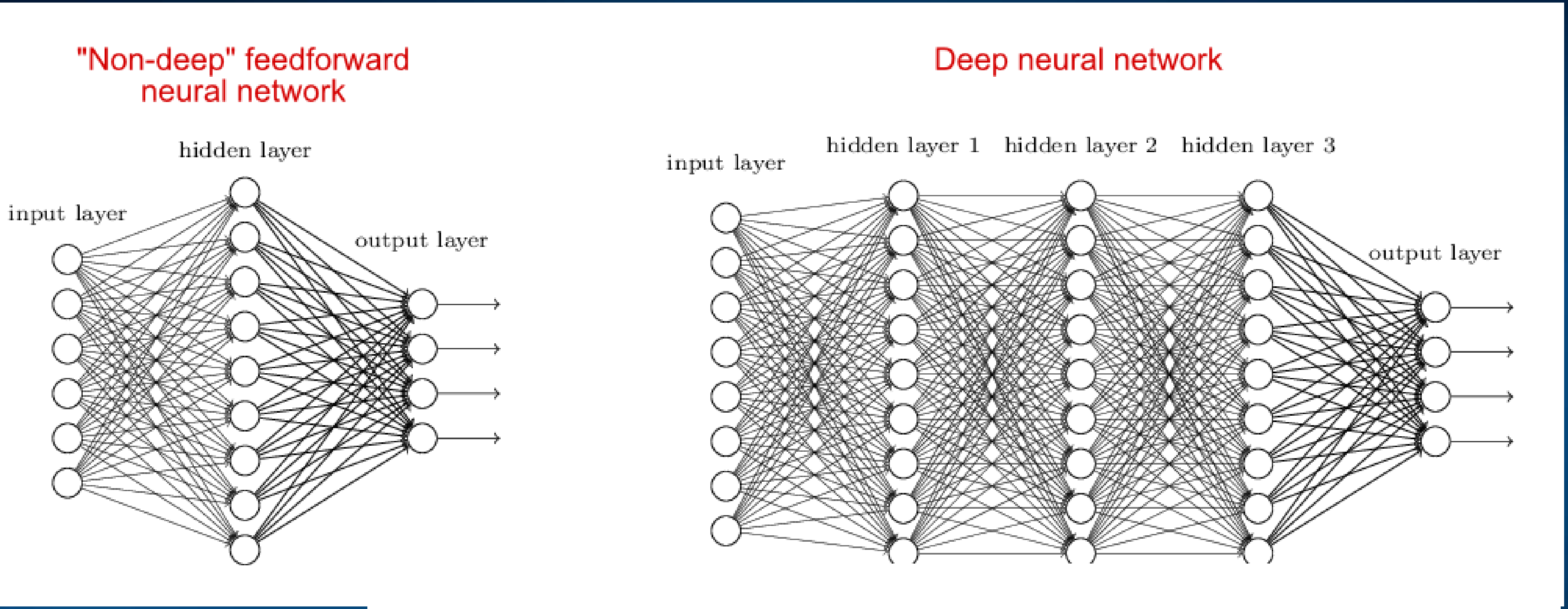




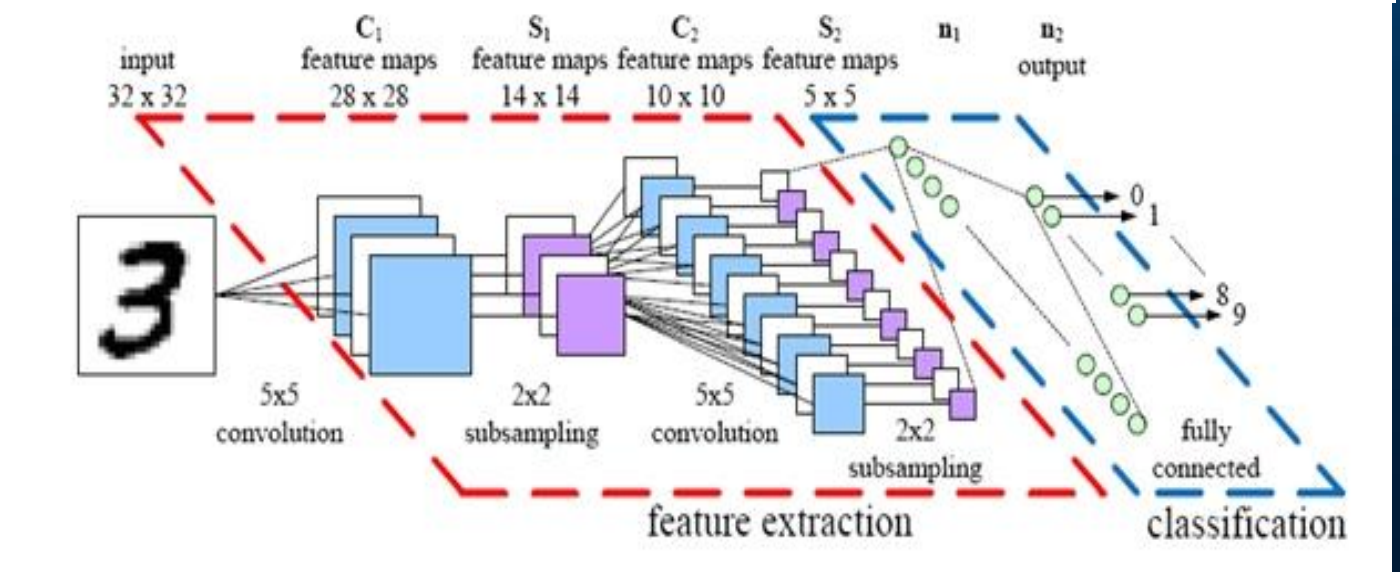


Exploratory and multi-way blind source separation and tensor factorizations: unsupervised learning methods and software to find the hidden causes & underlying hidden structure in the data.

Tensorization of Convolutive Deep Learning NN



A. Cichocki Lab
RIKEN BSI

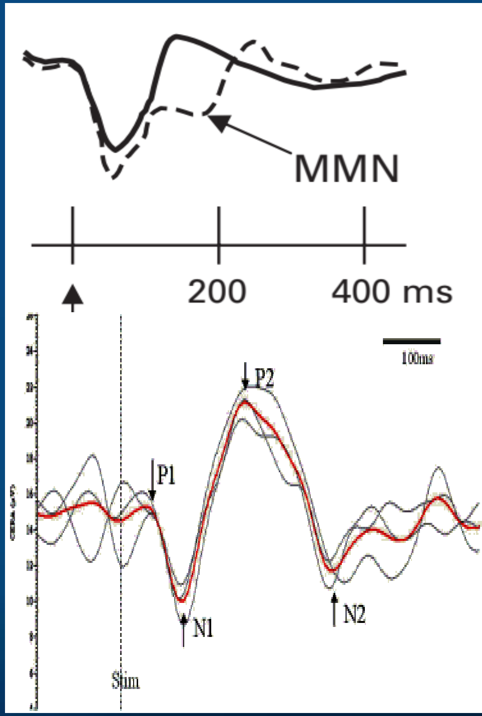


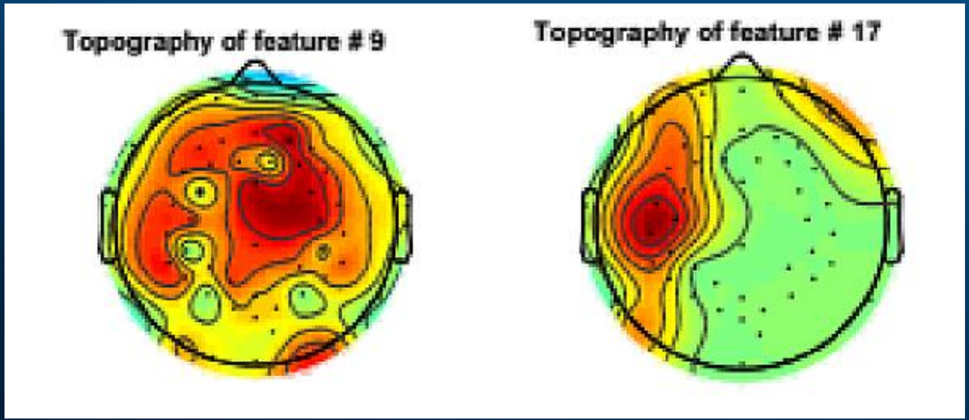
Infant EEG for phonematic hearing

"NeuroPerKog: development of phonematic hearing and working memory in infants and children", with the Institute of Physiology and Pathology of Hearing - analyze pathologies of central processing using EEG responses of infant brains (8-13 mo) to the native/non-native syllable speech sounds, see the effect of training.

Mismatch Negativity (MMN): event-related potential (ERP) component difference between standard and deviant stimuli.

Acoustic Change Complex (ACC) P1-N1-P2-N2 complex – response to multiple acoustic changes, reflects discrimination capacity in the absence of attention. Here standard/easy and standard/hard.



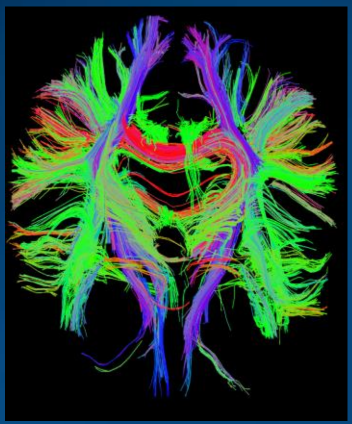


Non-negative Tucker tensor decomposition, spatial domain.

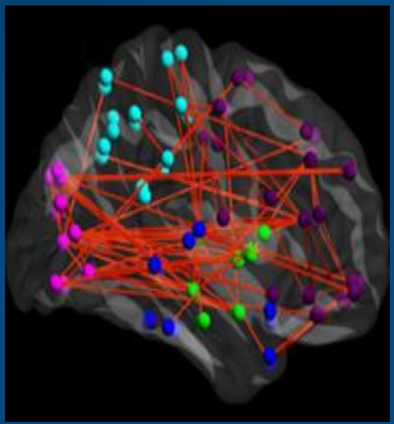
Brain connectivity for psychiatric diagnosis

Human connectome and MRI/fMRI

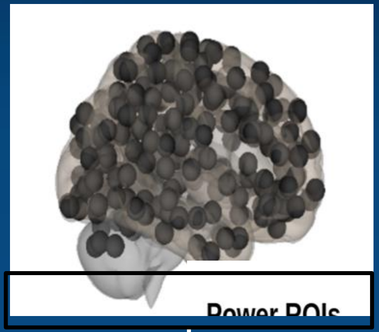
Structural connectivity



Functional connectivity

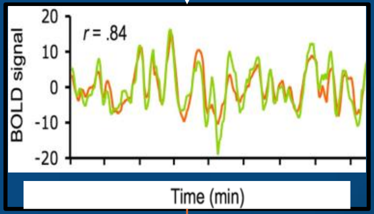


Node definition (parcelation)

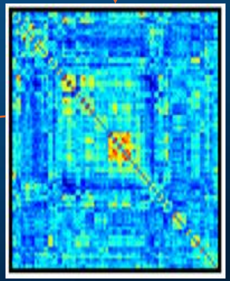


BOLD signal extraction

Correlation calculation

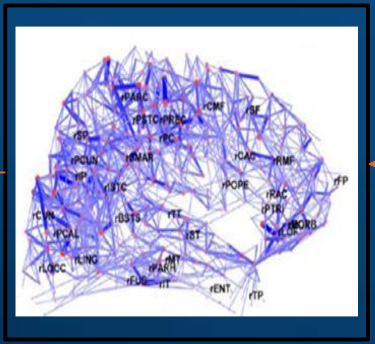


Correlation matrix

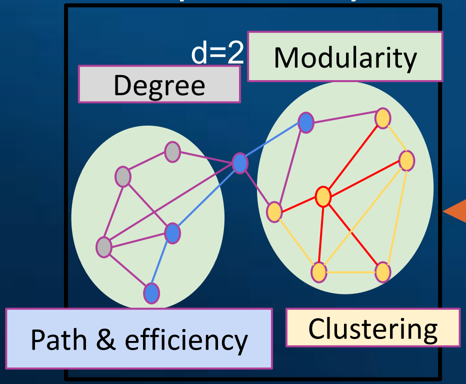


Binary matrix

Whole-brain graph



Graph theory



Many toolboxes available for such analysis.

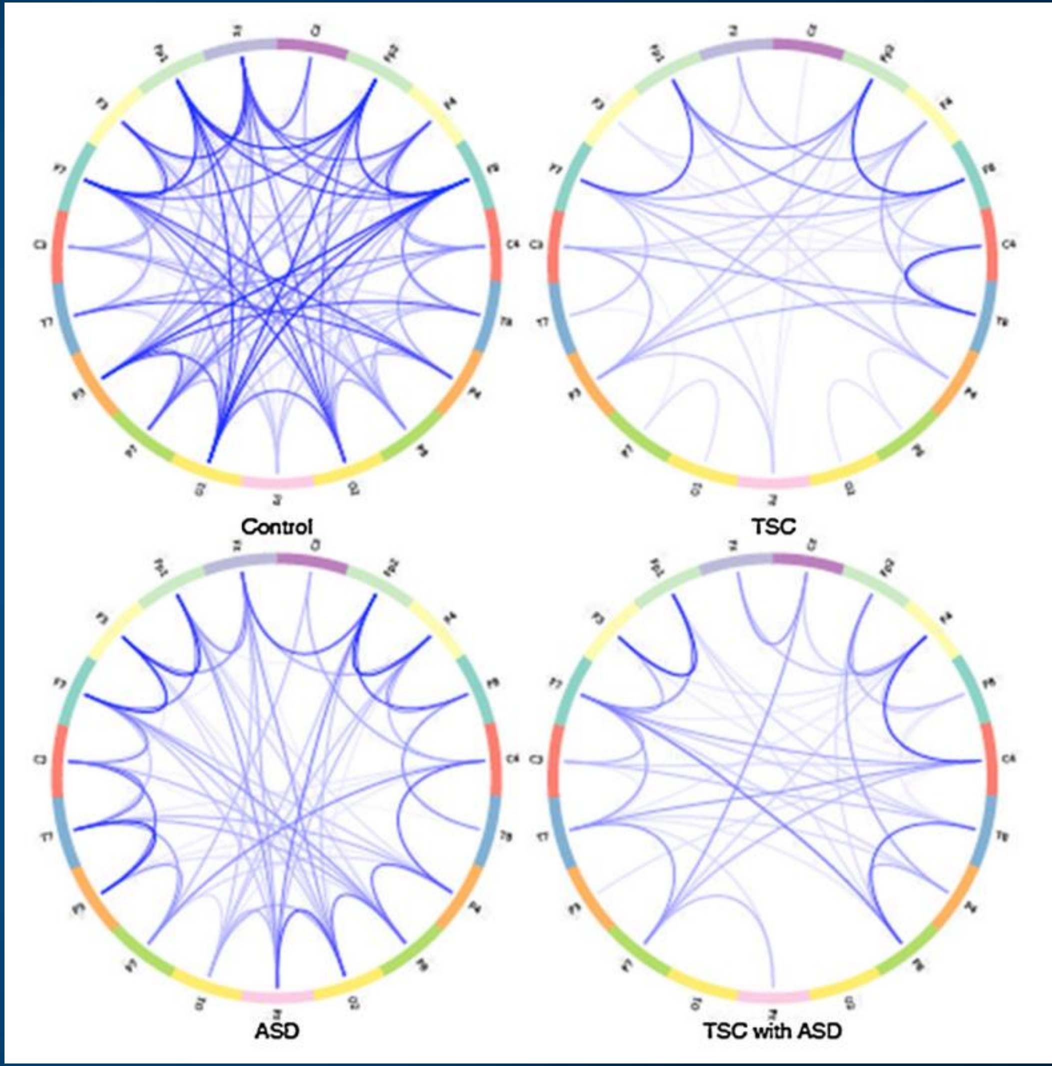
Bullmore & Sporns (2009)

ASD: pathological connections

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

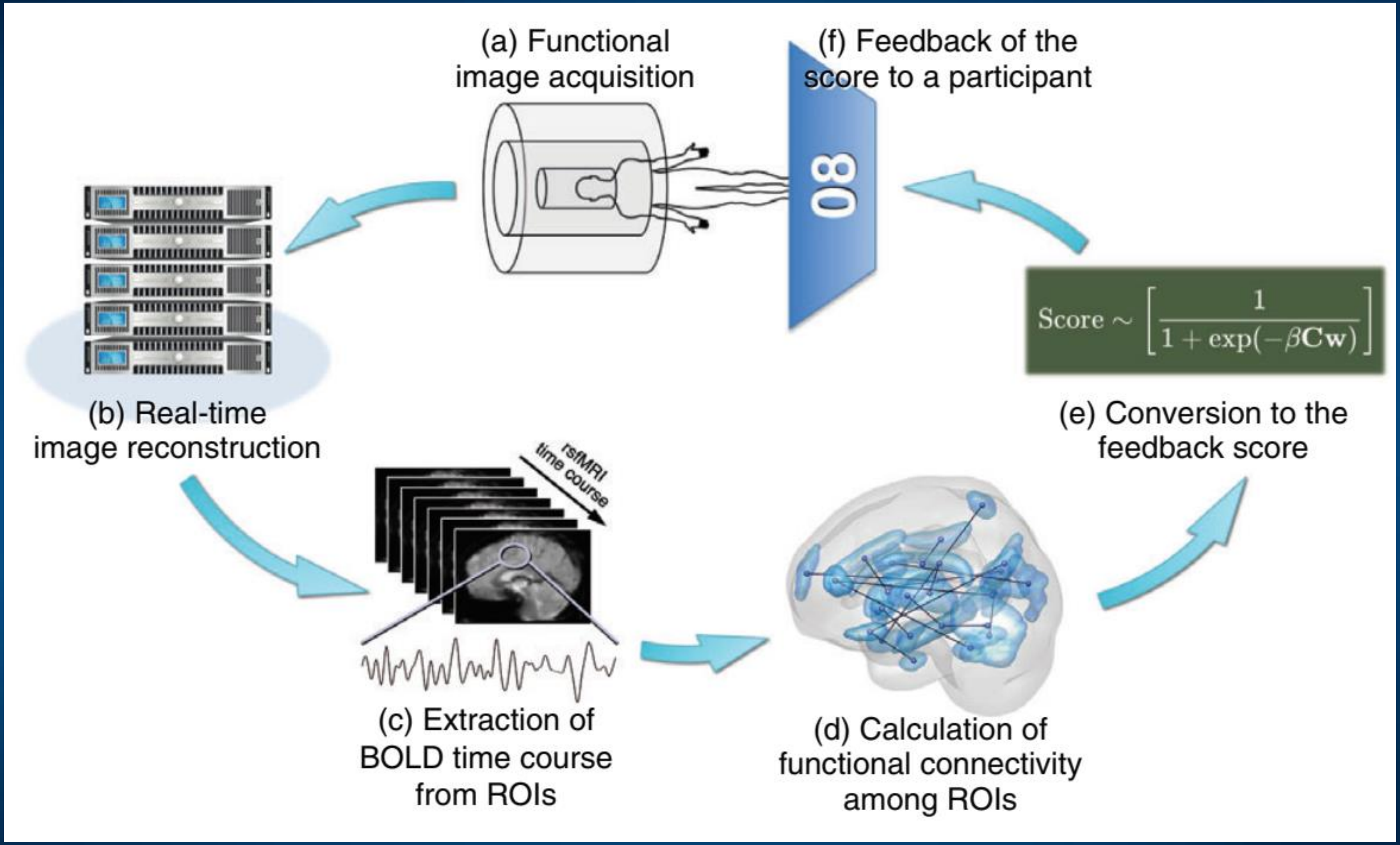
Coherence between electrodes. Weak or missing connections between distant regions prevent ASD/TSC patients from solving more demanding cognitive tasks.

Network analysis – info flow, diagnosis of changes due to the disease and learning; **correct your networks**!



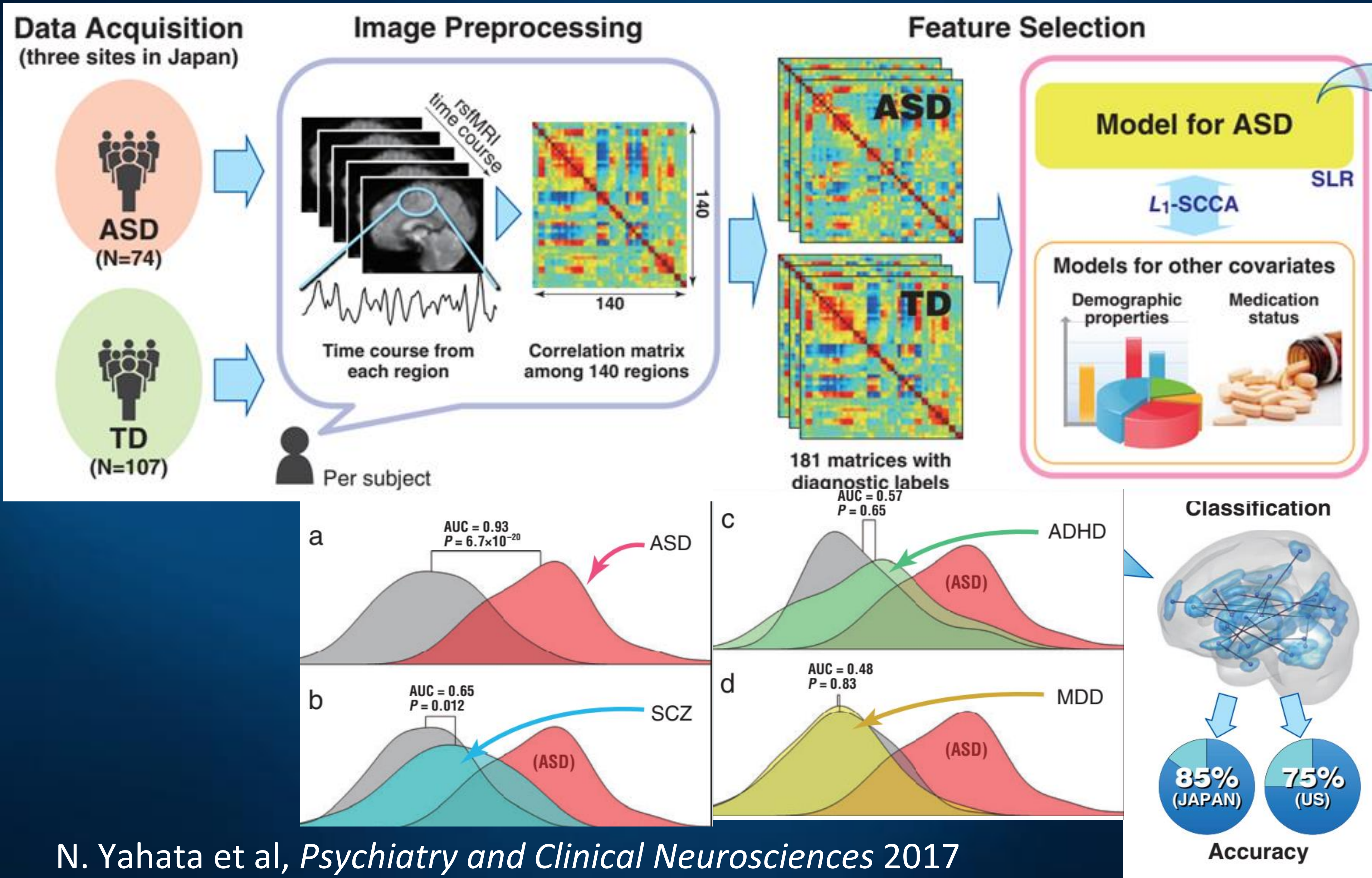
J.F. Glazebrook, R. Wallace, Pathologies in functional connectivity, feedback control and robustness. Cogn Process (2015) 16:1–16

Neurofeedback may repair network?



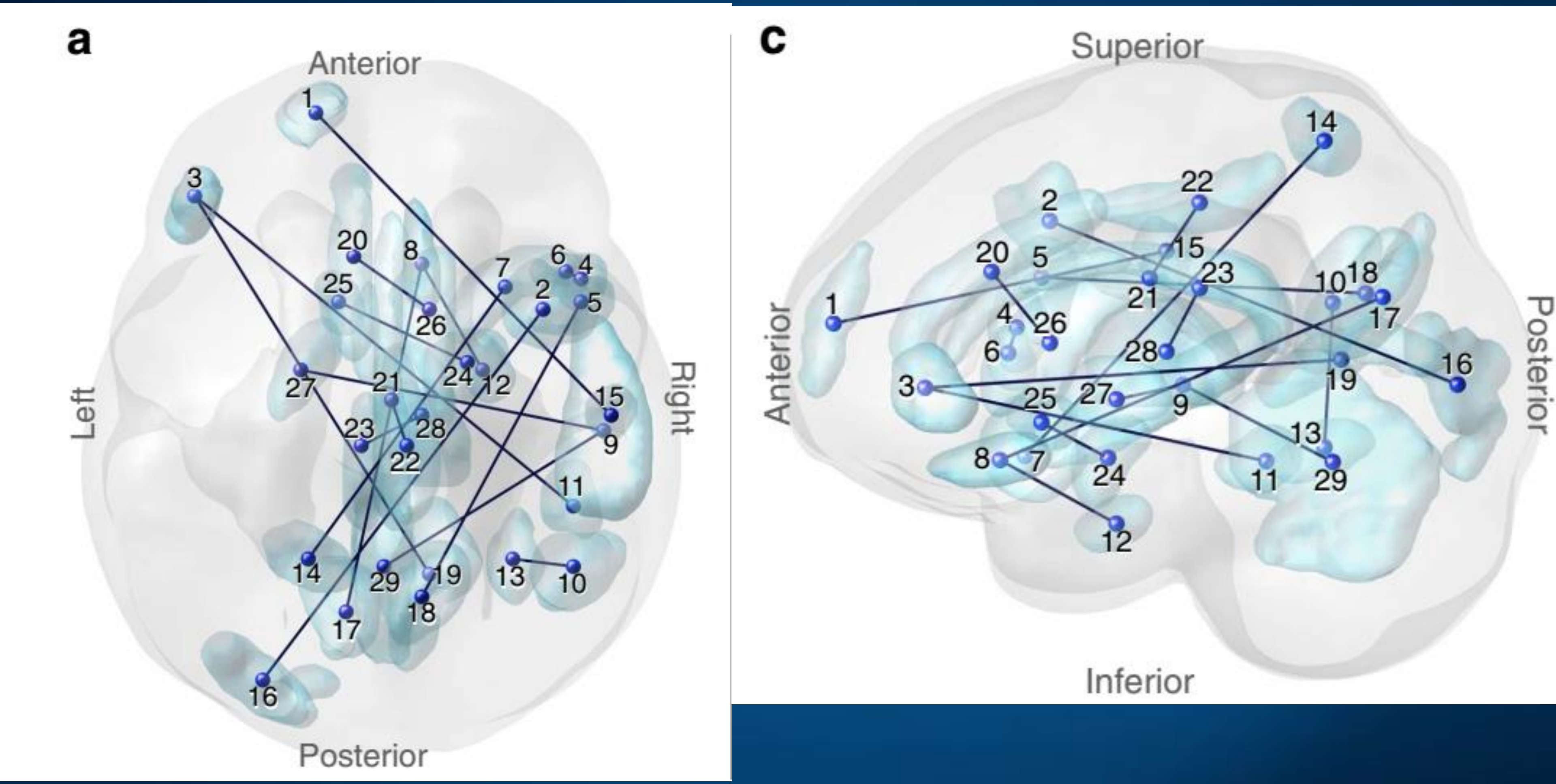
Megumi F, Yamashita A, Kawato M, Imamizu H. Functional MRI neurofeedback training on connectivity between two regions induces long-lasting changes in intrinsic functional network. *Front. Hum. Neurosci.* 2015; **9**: 160.

Diagnosis based on fMRI



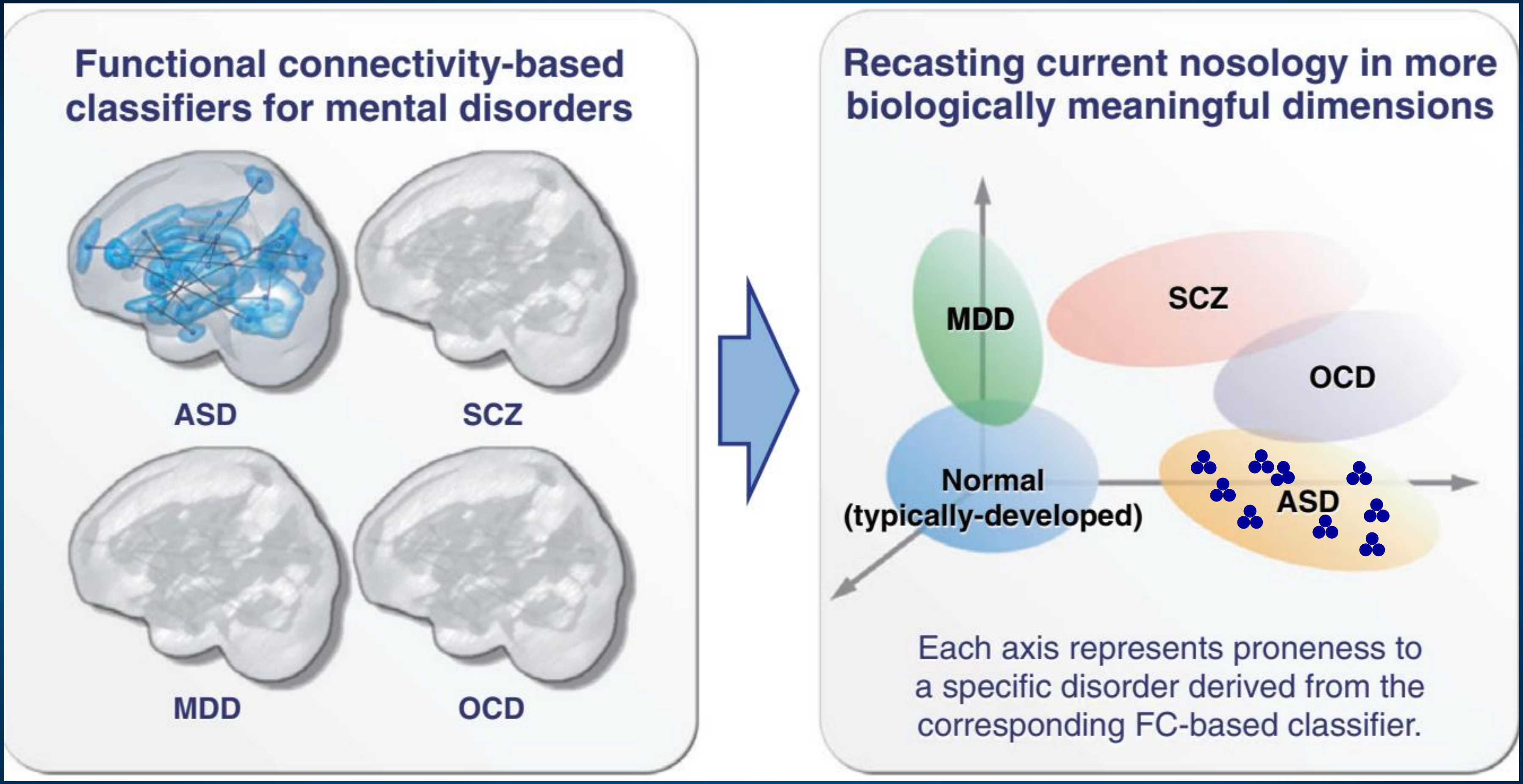
N. Yahata et al, *Psychiatry and Clinical Neurosciences* 2017

Selected connections



N. Yahata et al (2016): 29 selected regions (ROI) and 16 connections are 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 patients.

Propensity to 4 disorders



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

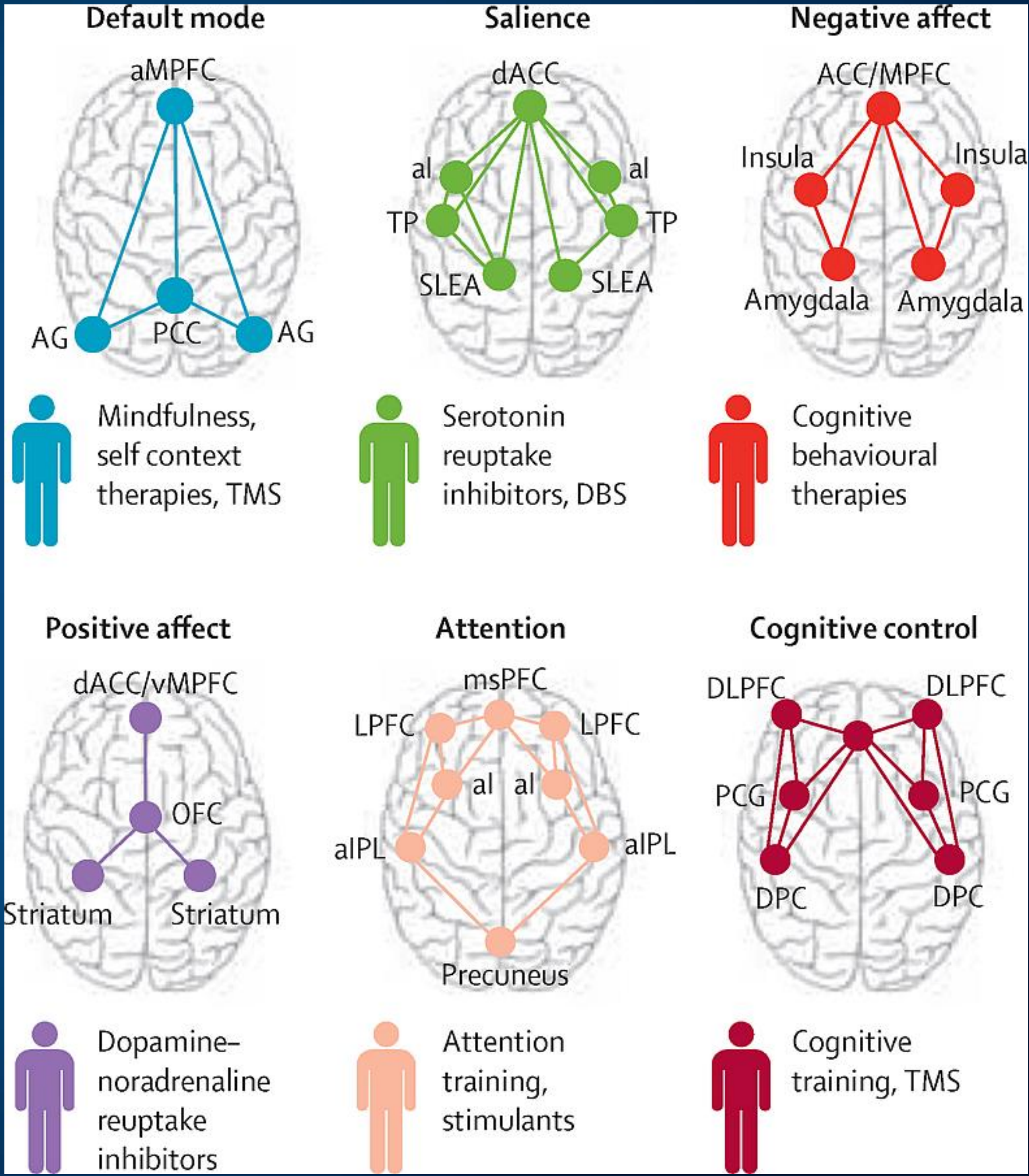
N. Yahata et al, *Psychiatry and Clinical Neurosciences* 2017; **71**: 215–237

Multi-level phenomics

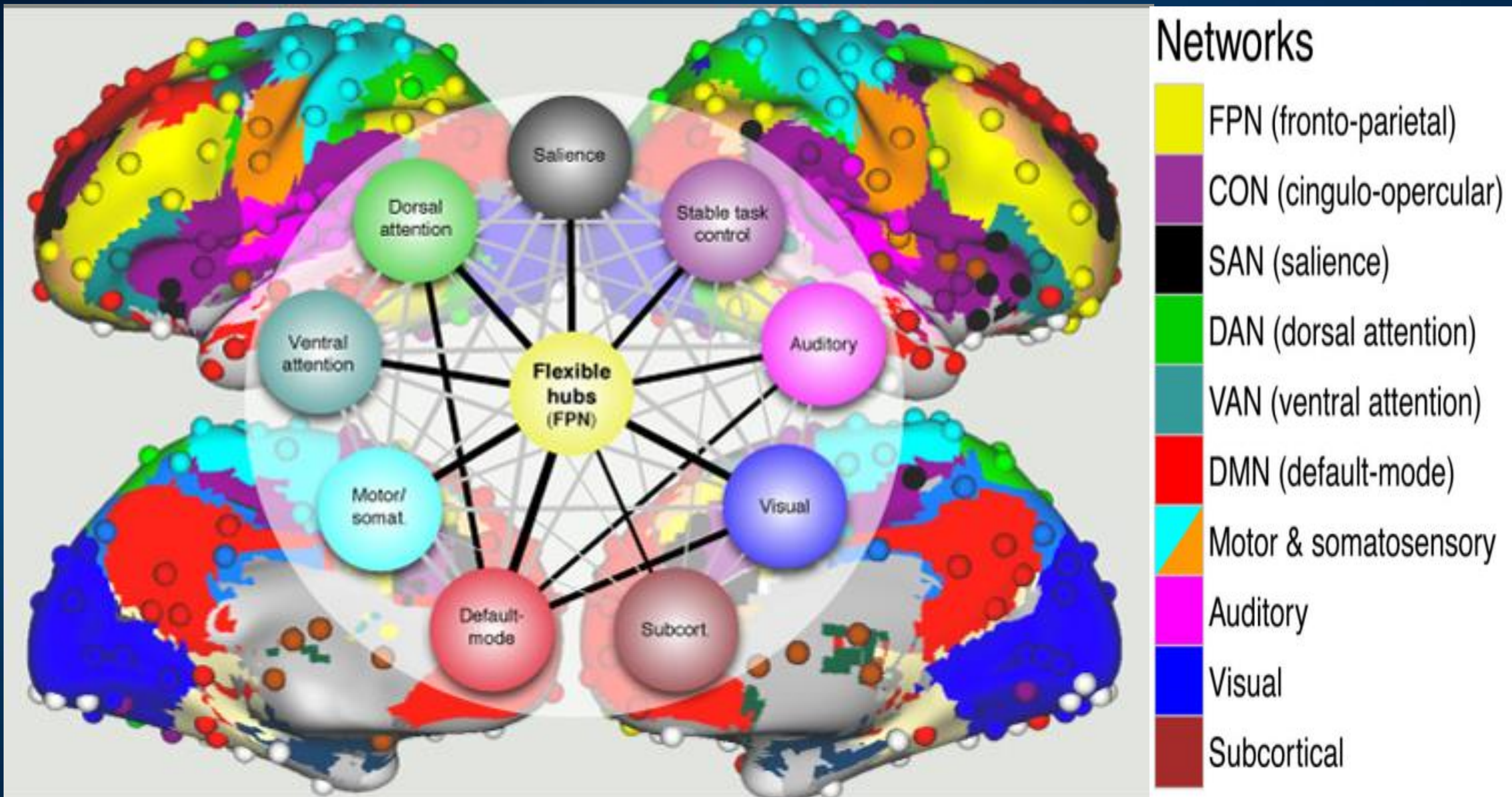
Instead of classification of mental disease by symptoms use **Research Domain Criteria** (RDoC) matrix based on **multi-level neuropsychiatric phenomics** describing large brain systems deregulation.

1. **Negative Valence Systems**,
2. **Positive Valence Systems**
3. **Cognitive Systems**
4. **Social Processes Systems**
5. **Arousal/Regulatory Systems**

Include genes, molecules, cells, **circuits**, physiology, behavior, self-reports and paradigms.



Neurocognitive Basis of Cognitive Control



Central role of fronto-parietal (FPN) flexible hubs in cognitive control and adaptive implementation of task demands (black lines=correlations significantly above network average). Cole et al. (2013).

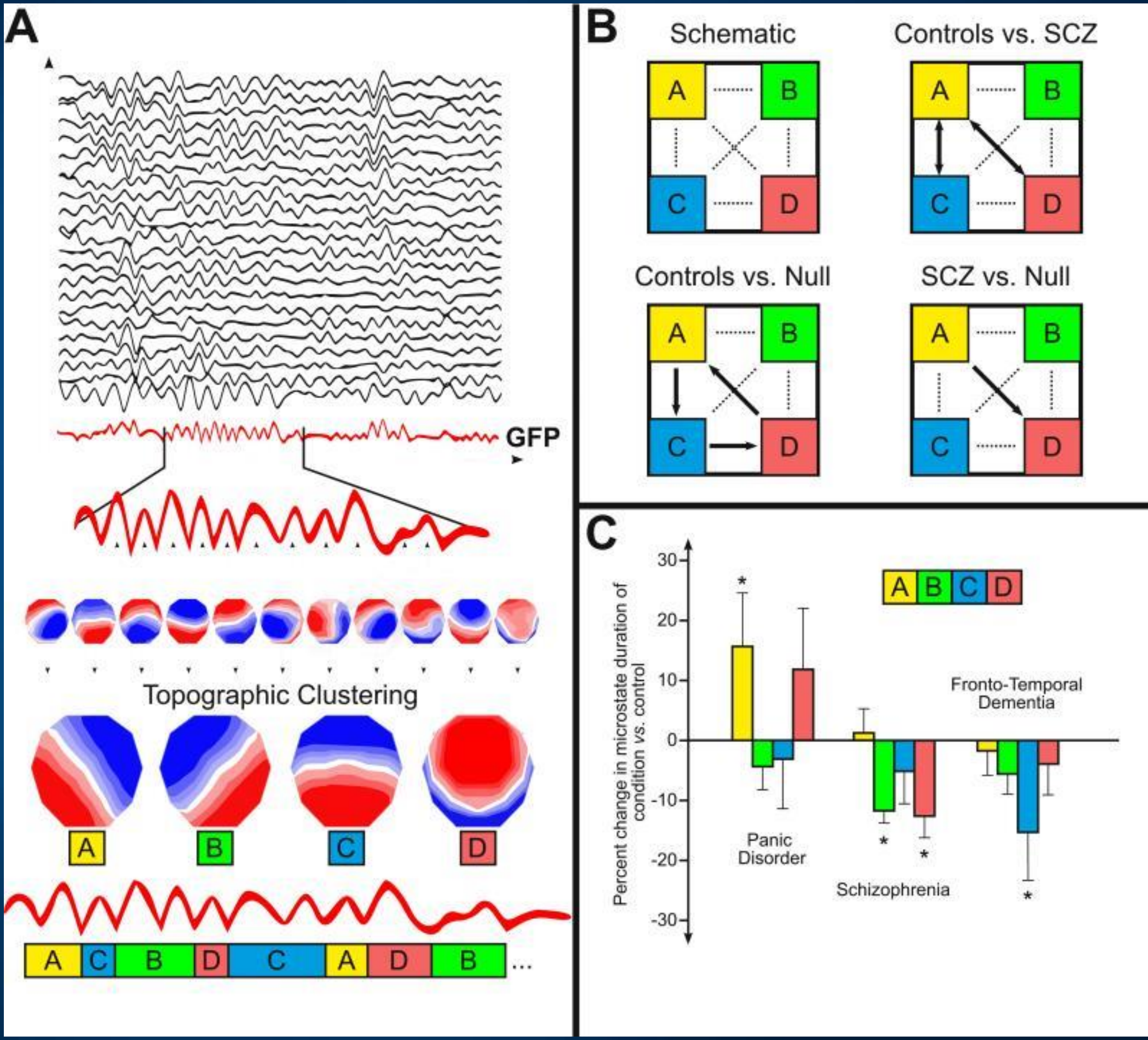
Brain networks are dynamic

Microstates

Lehmann et al.
EEG microstate duration and syntax in acute, medication-naïve, first-episode schizophrenia: a multi-center study.
Psychiatry Research Neuroimaging, 2005

Khanna et al.
Microstates in Resting-State EEG: Current Status and Future Directions.
Neuroscience and Biobehavioral Reviews, 2015

Symbolic dynamics.

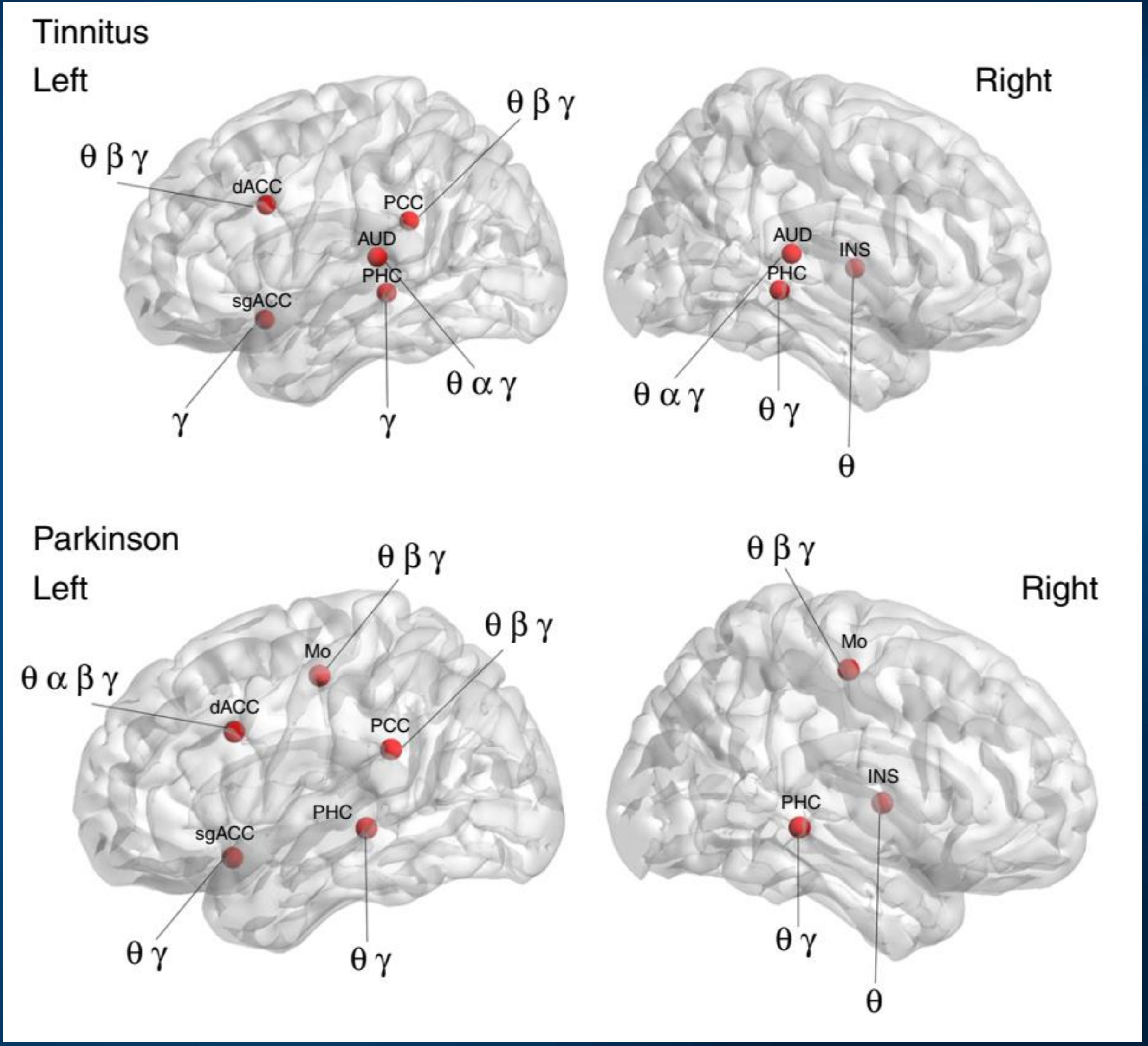


Thalamocortical dysrhythmia

Vanneste, S., Song, J.-J., & Ridder, D. D. Thalamocortical dysrhythmia (TCD) detected by machine learning. *Nature Communications*, *9*(1), 1103 (2018)

TCD: common oscillatory pattern in resting-state, α activity is replaced by cross-frequency coupling of θ and β, γ oscillations.

Spatially distinct sources.

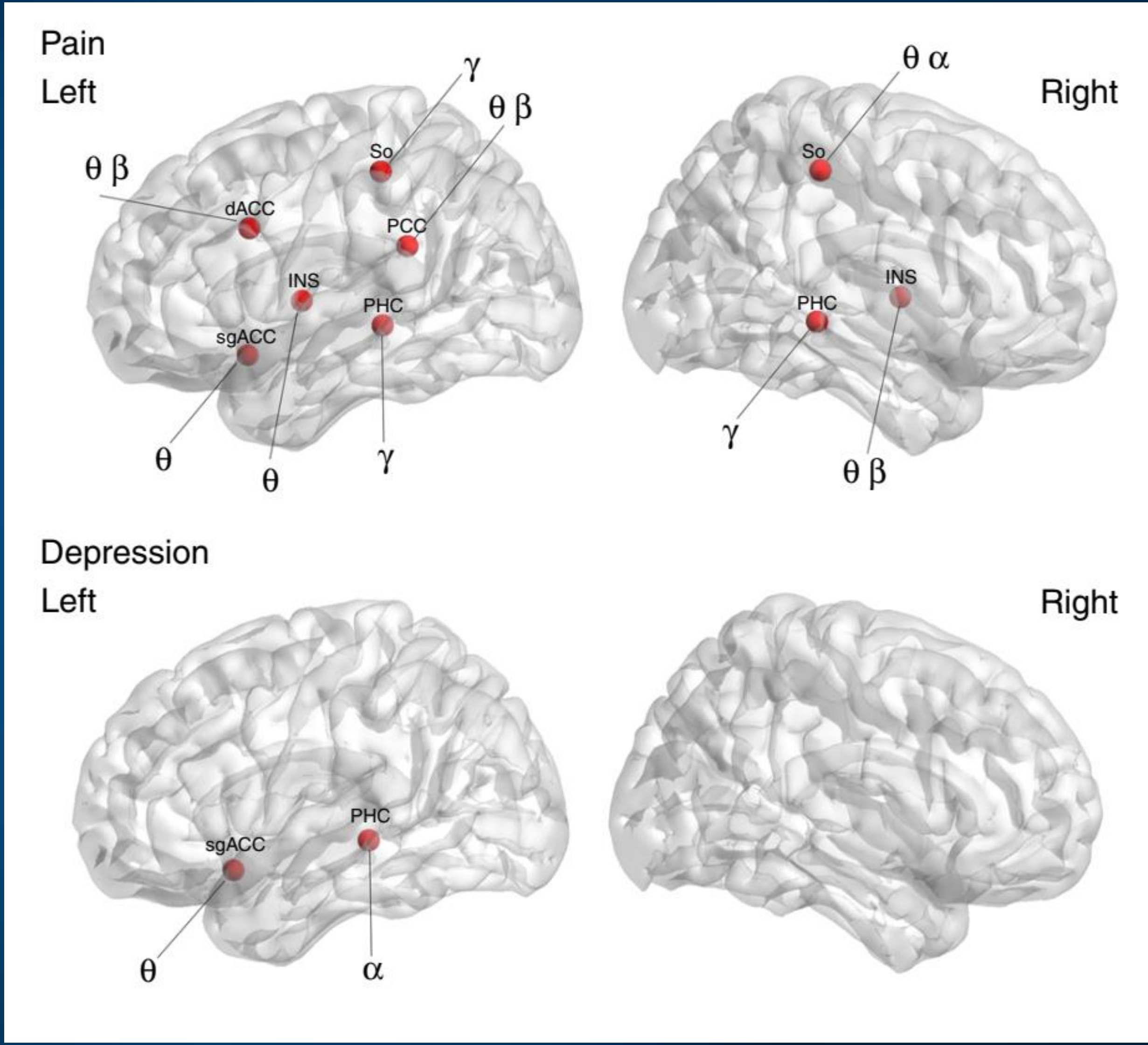


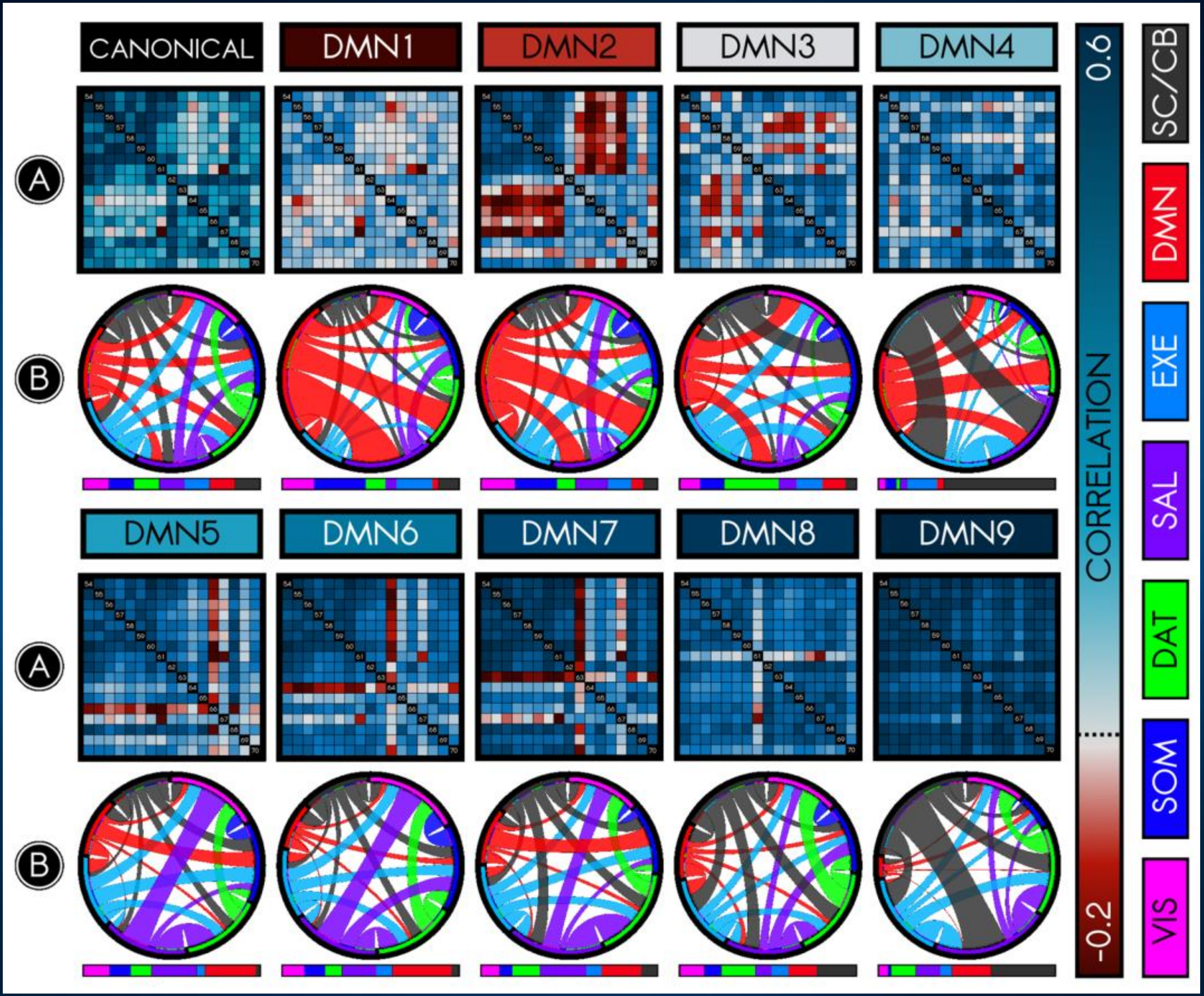
Thalamocortical dysrhythmia

Vanneste, S., Song, J.-J., & Ridder, D. D. *Nature Communications*, *9*(1), 1103 (2018)

TCD is common to the pathology of Parkinson's disease, pain, tinnitus, and depression.

Source localization with sLORETA + SVM selection of regions and shows different regions and frequency bands for different disease.





CANONICAL
DMN1
DMN2
DMN3
DMN4
DMN5
DMN6
DMN7
DMN8
DMN9
A
B
CORRELATION
0.6
-0.2
SC/CB
DMN
EXE
SAL
DAT
SOM
VIS

Data workflow

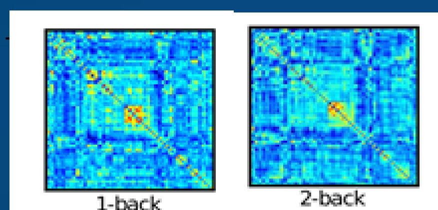
Two experimental conditions: 1-back, 2-back

Node definition

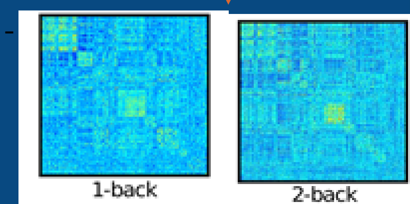
Anatomical parcellation (**90** nodes)

Functional parcellation (**264** nodes)

Weighted correlation matrices

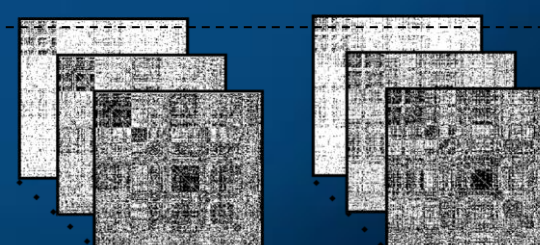


Fisher's *z*-scores



Binary correlation matrices

Threshold (0.01 - 0.6)



global efficiency | local efficiency | modularity

Brain modules and cognitive processes

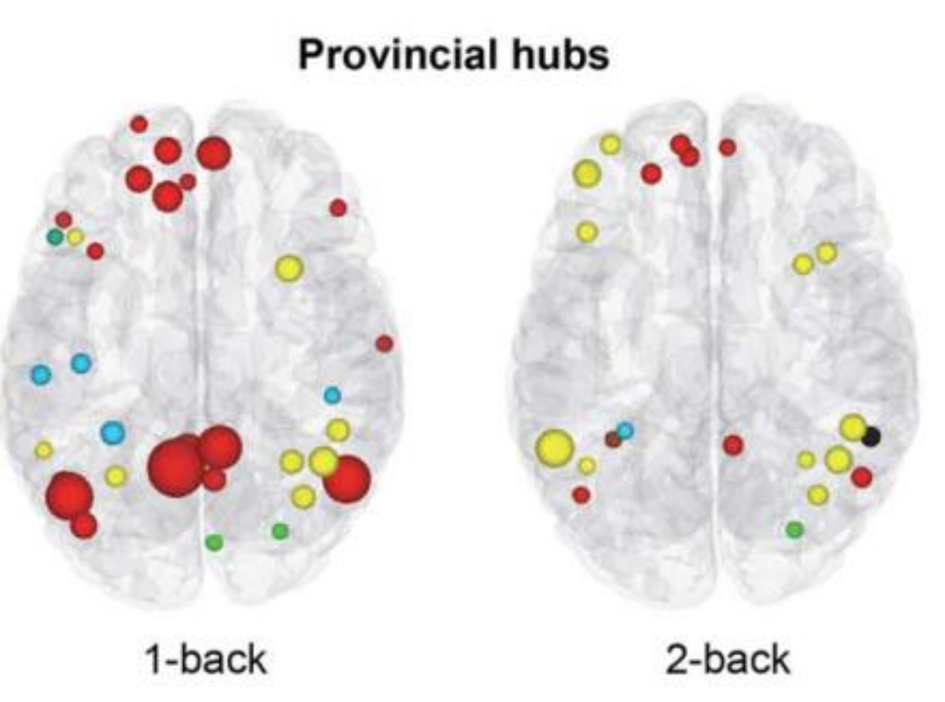
Simple and more difficult tasks, requiring the whole-brain network reorganization.

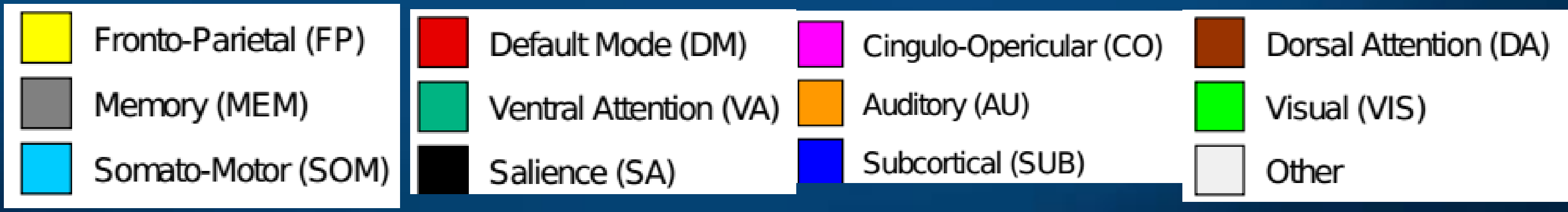
Left: 1-back local hubs

Right: 2-back local hubs

Average over 35 *participants.*

Dynamical change of the landscape of attractors, depending on the cognitive load. Less local (especially in DMN), more global binding (especially in PFC).





Finc K, Bonna K, Lewandowska M, Wolak T, Nikadon J, Dreszer J, Duch W, Kühn S. (2017) Transition of the functional brain network related to increasing cognitive demands. Human Brain Mapping 38(7), 3659–3674

Brain modules and cognitive processes

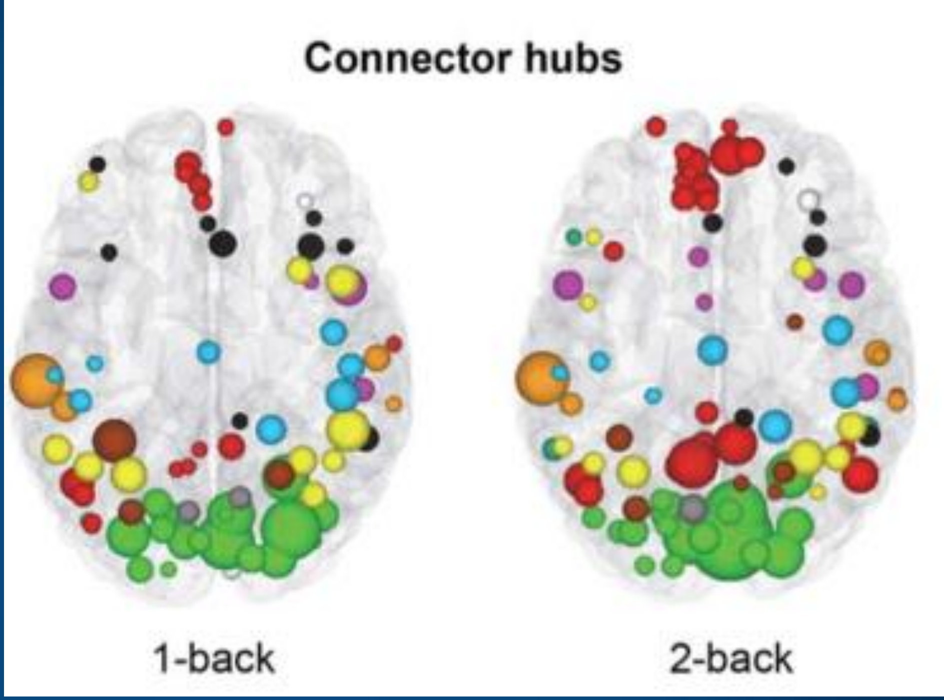
Simple and more difficult tasks, requiring the whole-brain network reorganization.

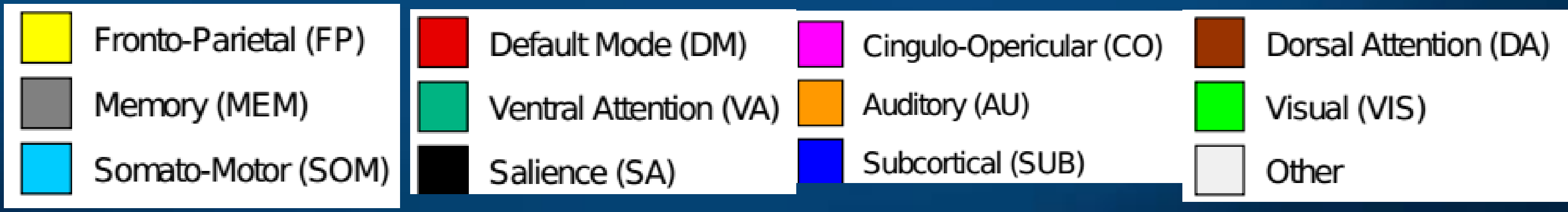
Left: 1-back connector hubs

Right: 2-back connector hubs

Average over 35 *participants.*

Dynamical change of the landscape of attractors, depending on the cognitive load – System 2 (Khaneman).
DMN areas engaged in global binding!

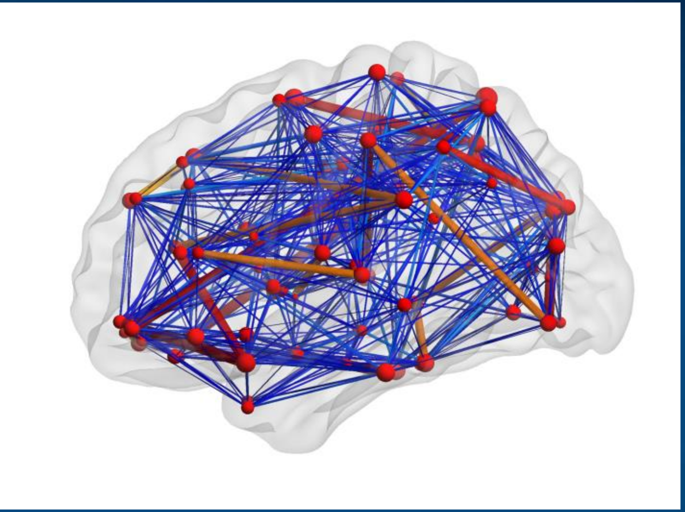


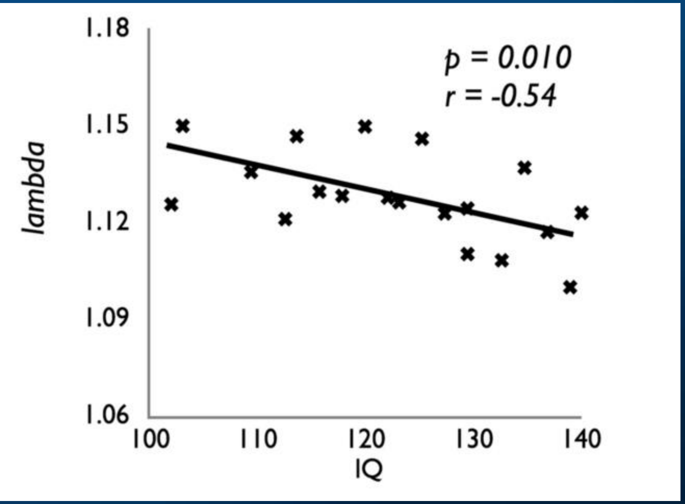


K. Finc et al, HBM (2017).

Resting state/cognitive performance

- Shorter path length λ → Higher intellectual performance
- Modularity → Working memory performance
- Modularity → Working memory capacity





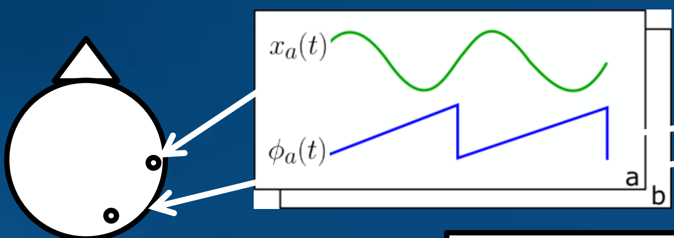
Network modularity ⇔ higher working memory capacity and performance.

High connectivity within modules and sparse connections between modules increases effective cooperation of brain regions, is associated with higher IQ.

van den Heuvel *et al.* (2009) | Stevens *et al.* (2012)

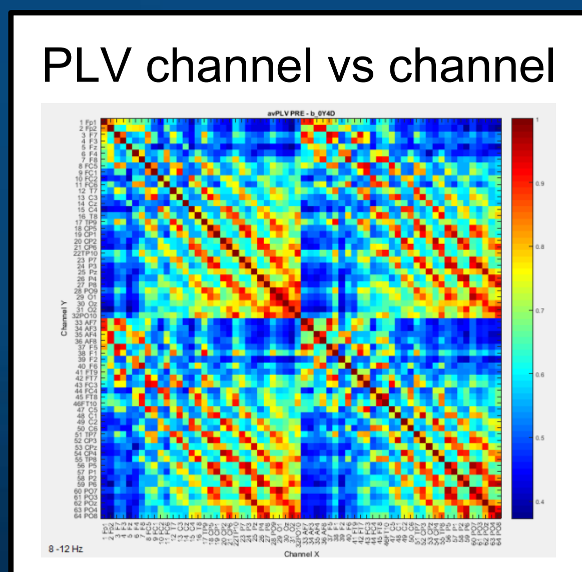
Functional connectivity changes

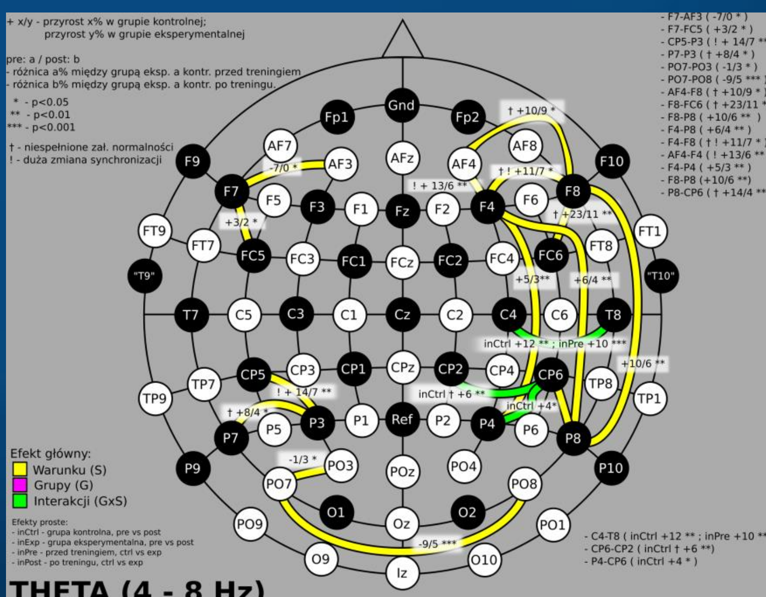
Influence of brain games on functional connectivity: **Phase Locking Value** (Burgess, 2013; Lachaux 1999), phase differences between signals measured at each electrode. PLV => synchronization maps, info flow.



$$\Phi(t) = \phi_a(t) - \phi_b(t)$$

$$PLV(a,b) = \frac{1}{T}\left|\sum_{t}^{T} e^{i\Phi(t)}\right|$$





Fingerprints of Mental Activity and non-linear dynamics

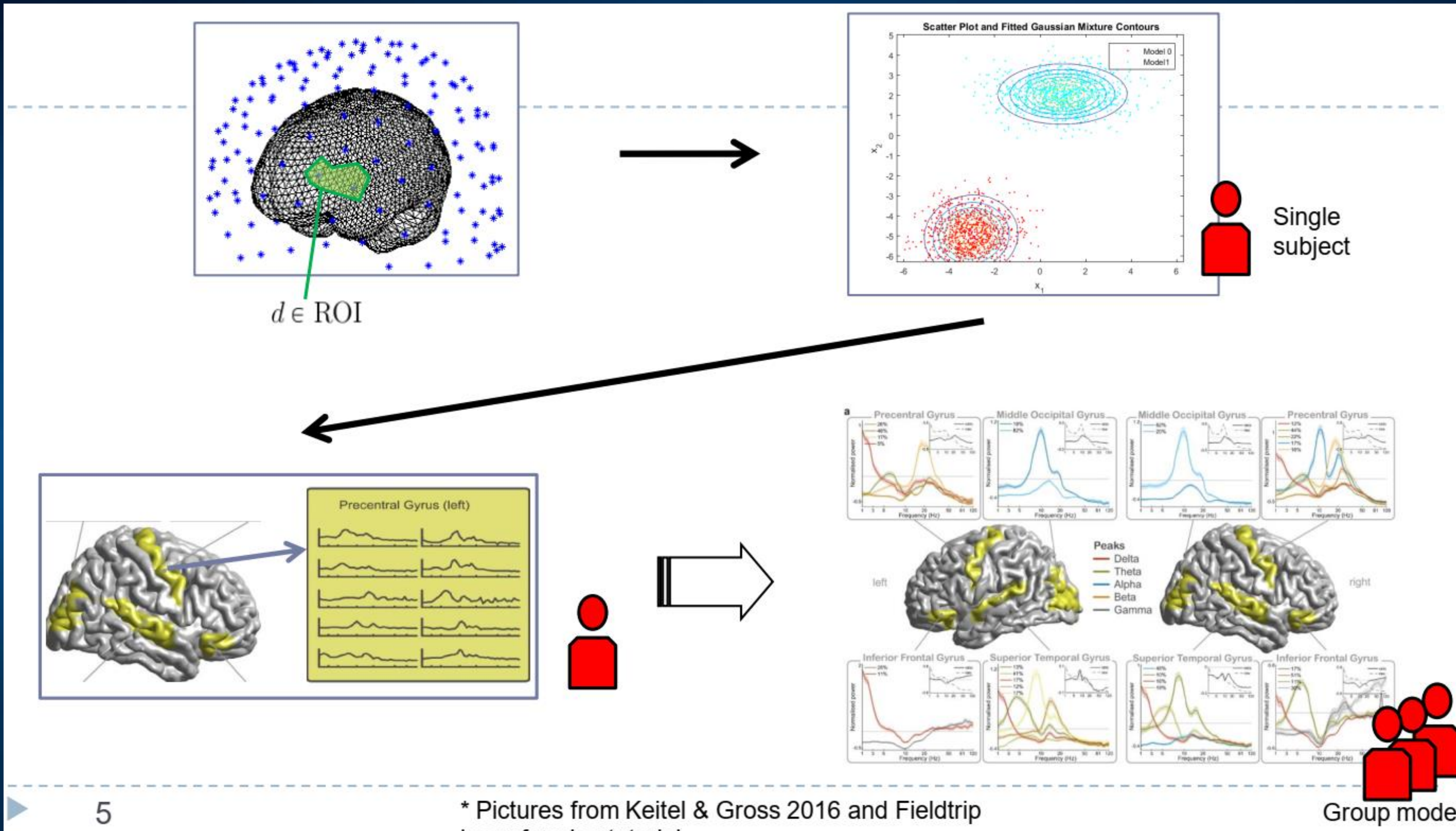
Possible form of Brain Fingerprints

fMRI: BFP is based on **V(X,t)** voxel intensity of fMRI BOLD signal changes, contrasted between task and reference activity or resting state.
EEG: spatial, spatio-temporal, ERP maps/shapes, coherence, various phase synchronization indices.

1. **Spectral fingerprinting** (MEG, EEG), power distributions.
2. **Spatial/Power**: direct localization/reconstruction of sources.
3. **Spatial/Synch**: changes in functional graph network structure.
4. **Frequency/Power**: ERS/ERD smoothed patterns E(X,t,f).
5. **ERP power maps**: spatio-temporal averaged energy distributions.
6. **EEG decomposition into components:** ICA, CCA, tensor, RP ...
7. **EEG** microstates, sequences & transitions, dynamics in ROI space.
8. Model-based: **The Virtual Brain**, integrating EEG/neuroimaging data.

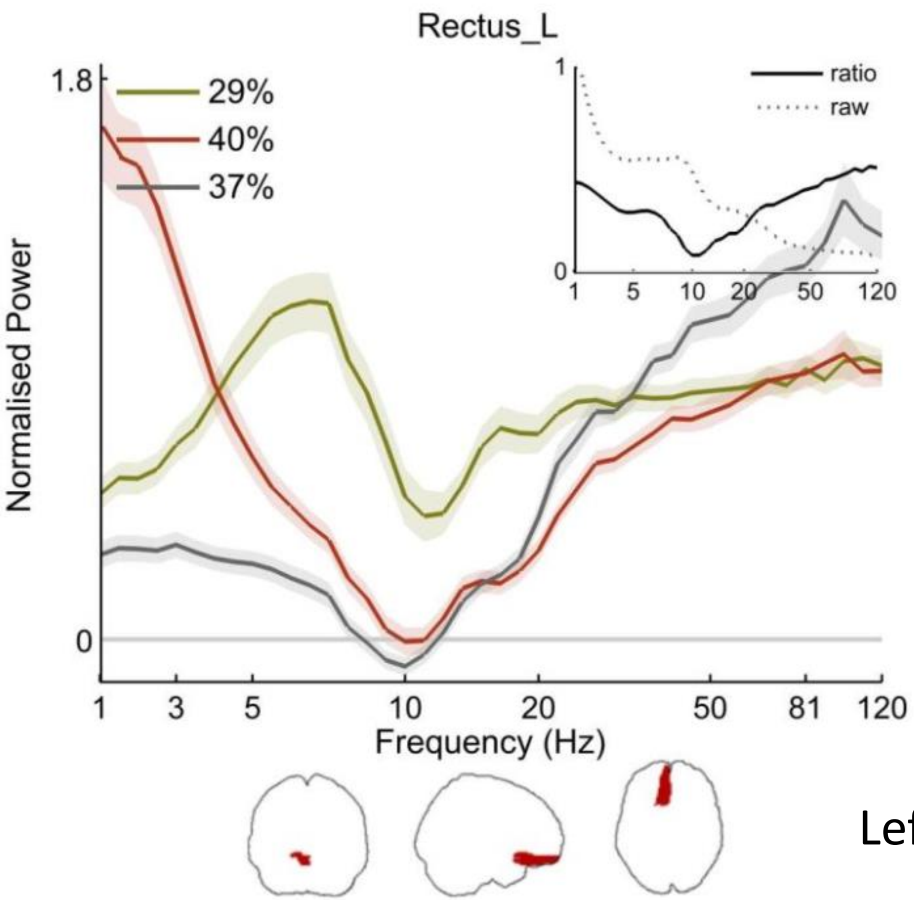
Neuroplastic changes of connectomes and functional connections as results of training for optimization of brain processes.

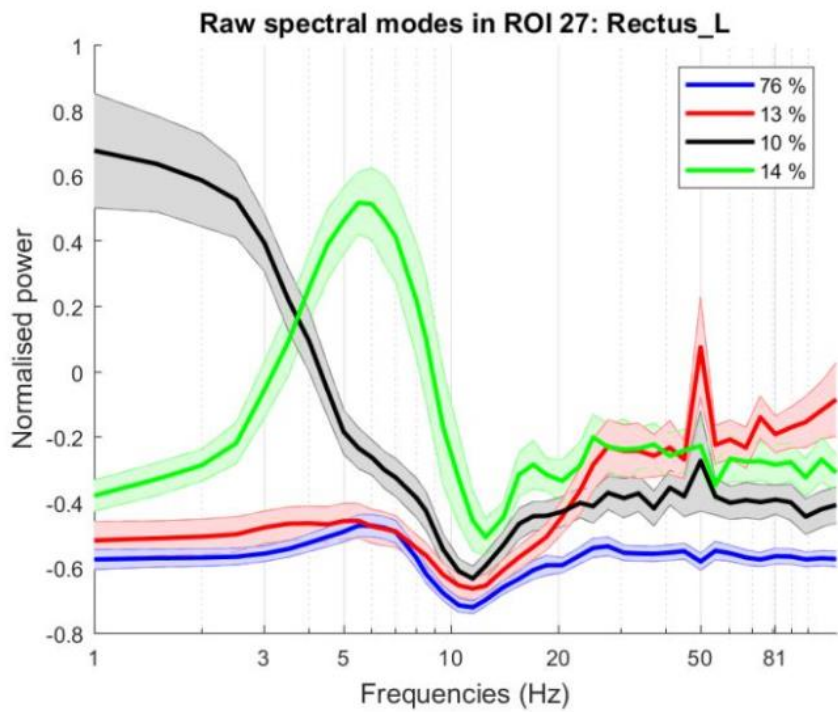
Spectral fingerprints



A. Keitel i J. Gross, „Individual human brain areas can be identified from their characteristic spectral activation fingerprints", *PLoS Biol* 14(6), e1002498, 2016

Spectral fingerprints





Left gyrus rectus

A. Keitel i J. Gross, „Individual human brain areas can be identified from their characteristic spectral activation fingerprints”, *PLoS Biol* 14, e1002498, 2016

Model of reading & dyslexia

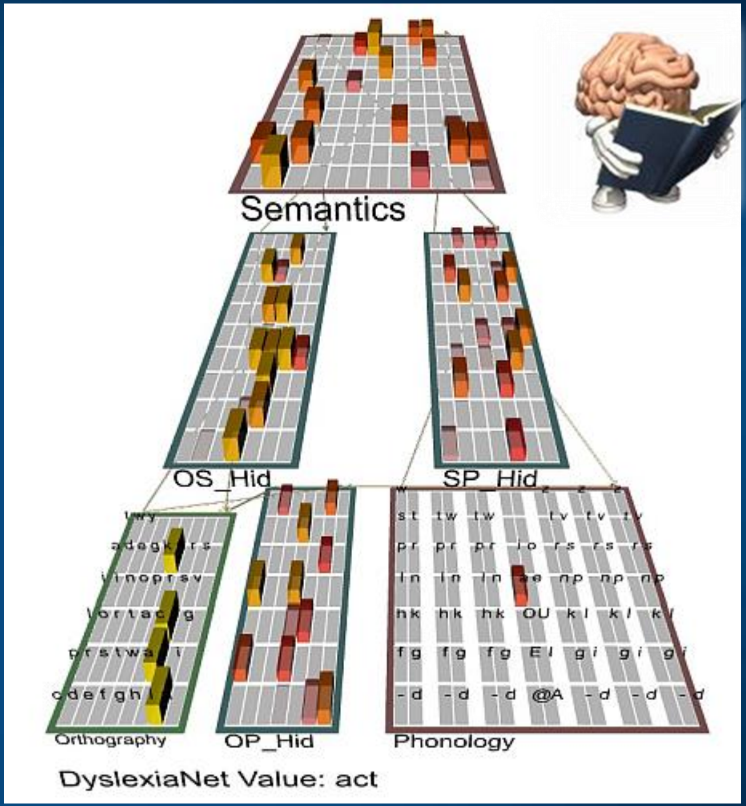
Emergent neural simulator:

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

3-layer model of reading:

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

In the brain: microfeature=subnetwork.
Hidden layers OS/OP/SP_Hid in between.

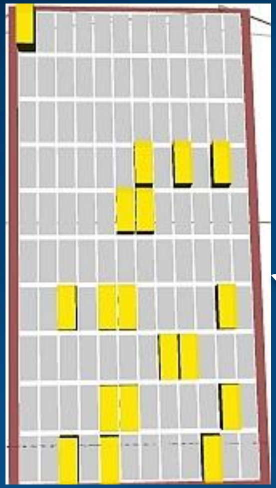


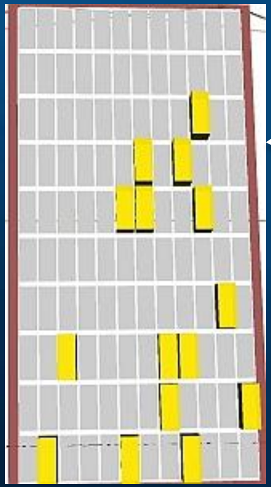
Learning: mapping one of the 3 layers to the other two.

Fluctuations around final configuration = attractors representing concepts.

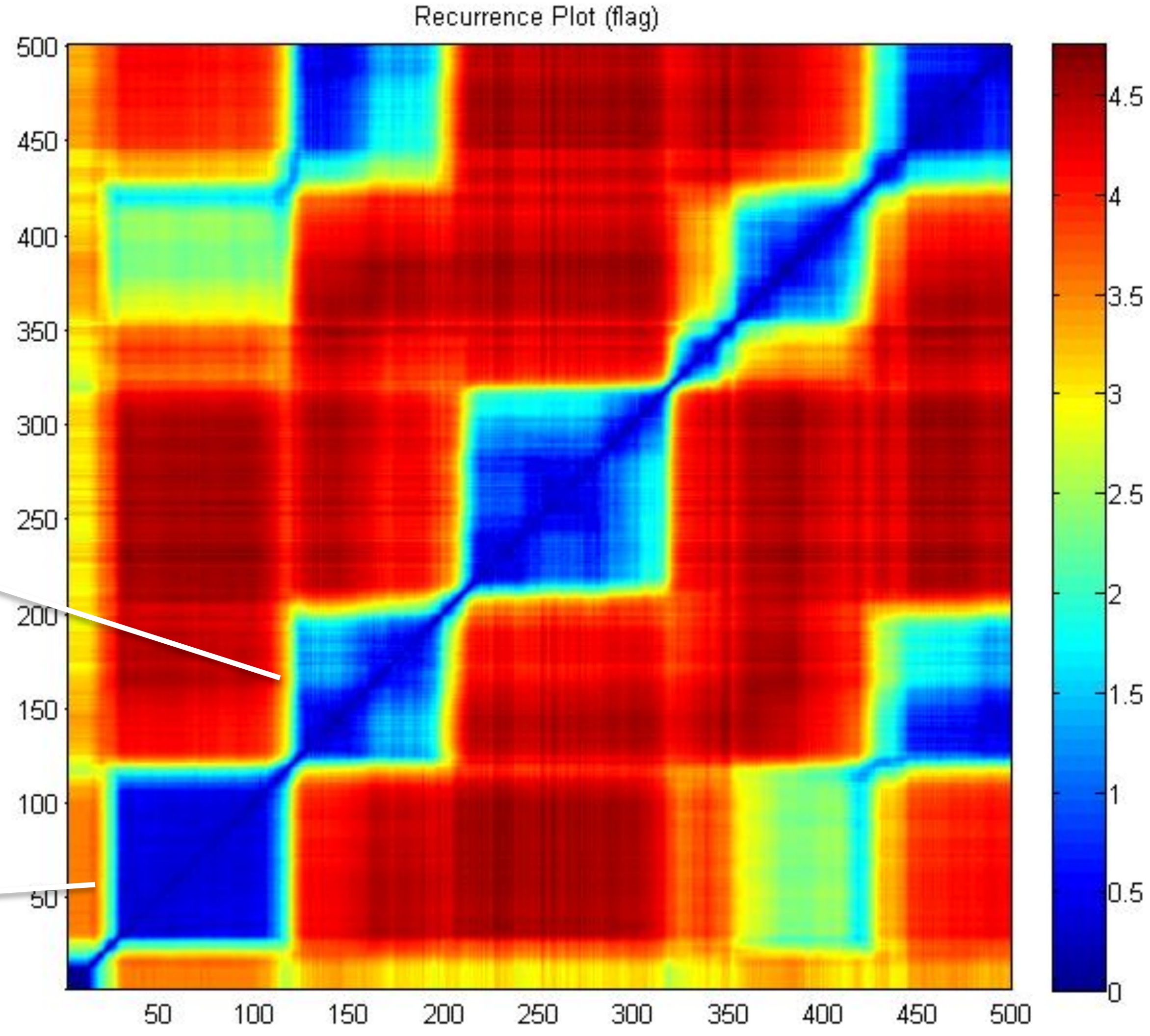
How to see properties of their basins, their relations?
Model in **Genesis**: more detailed neuron description.

rope



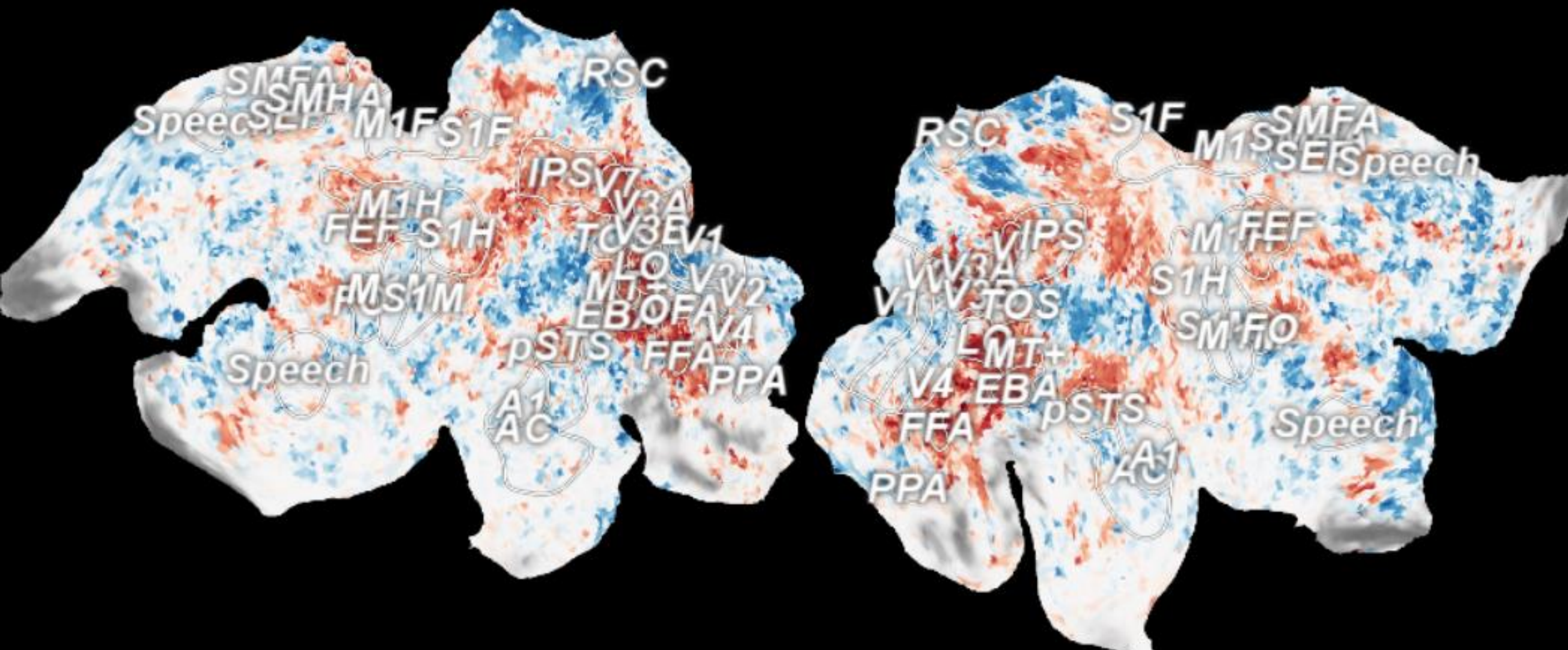


flag

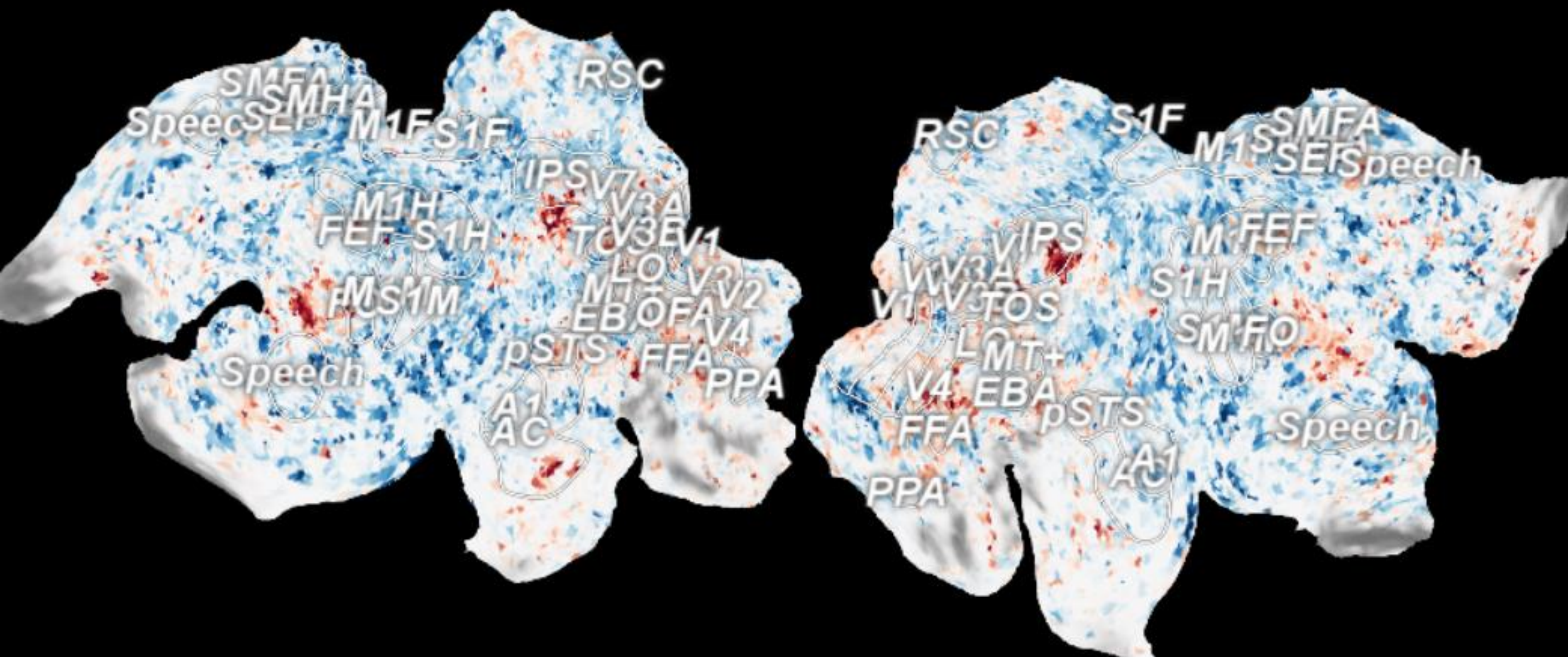


Transitions to new patterns that share some active units (microfeatures) shown in recurrence plots.

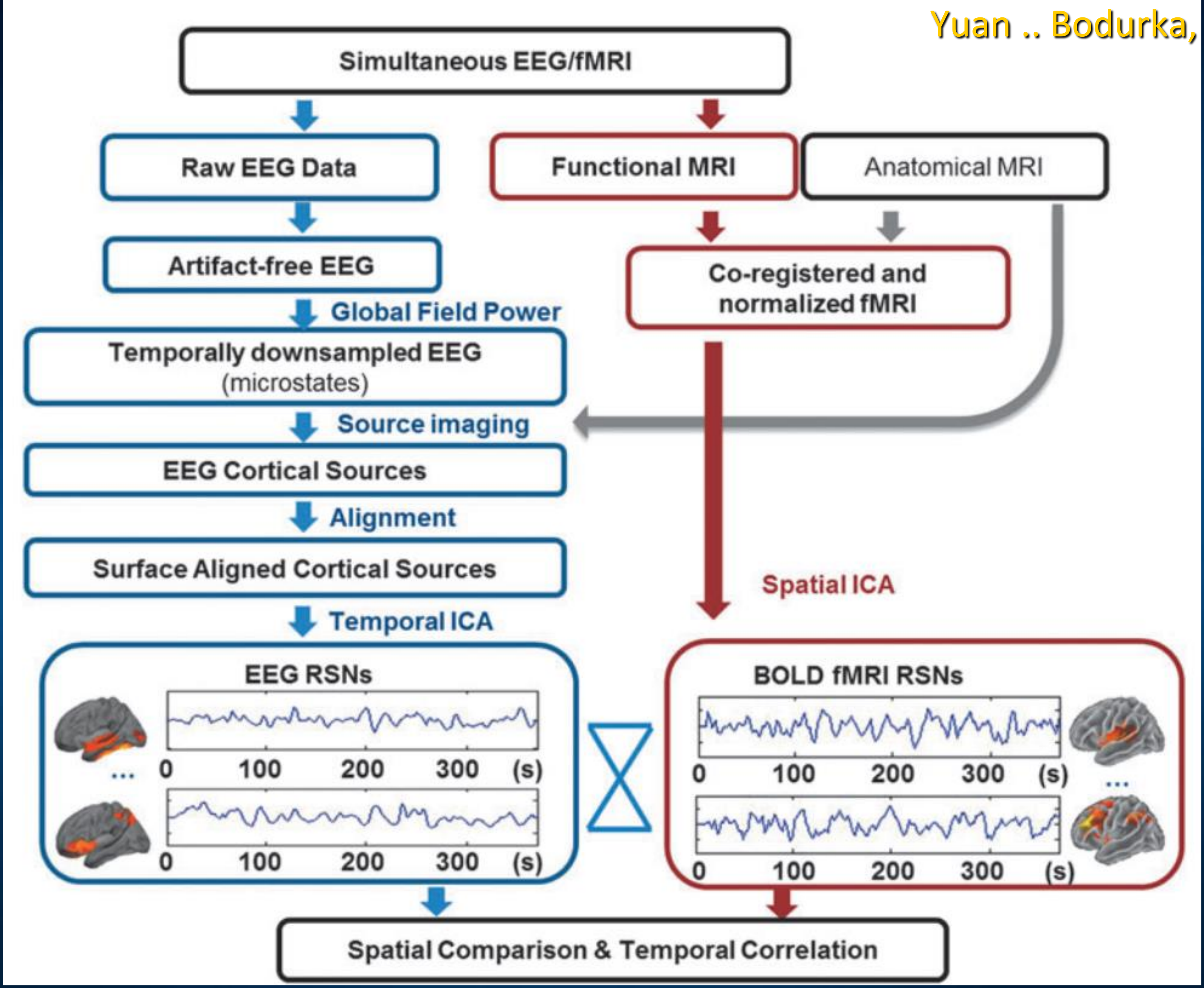
Category zebra: Passive Viewing



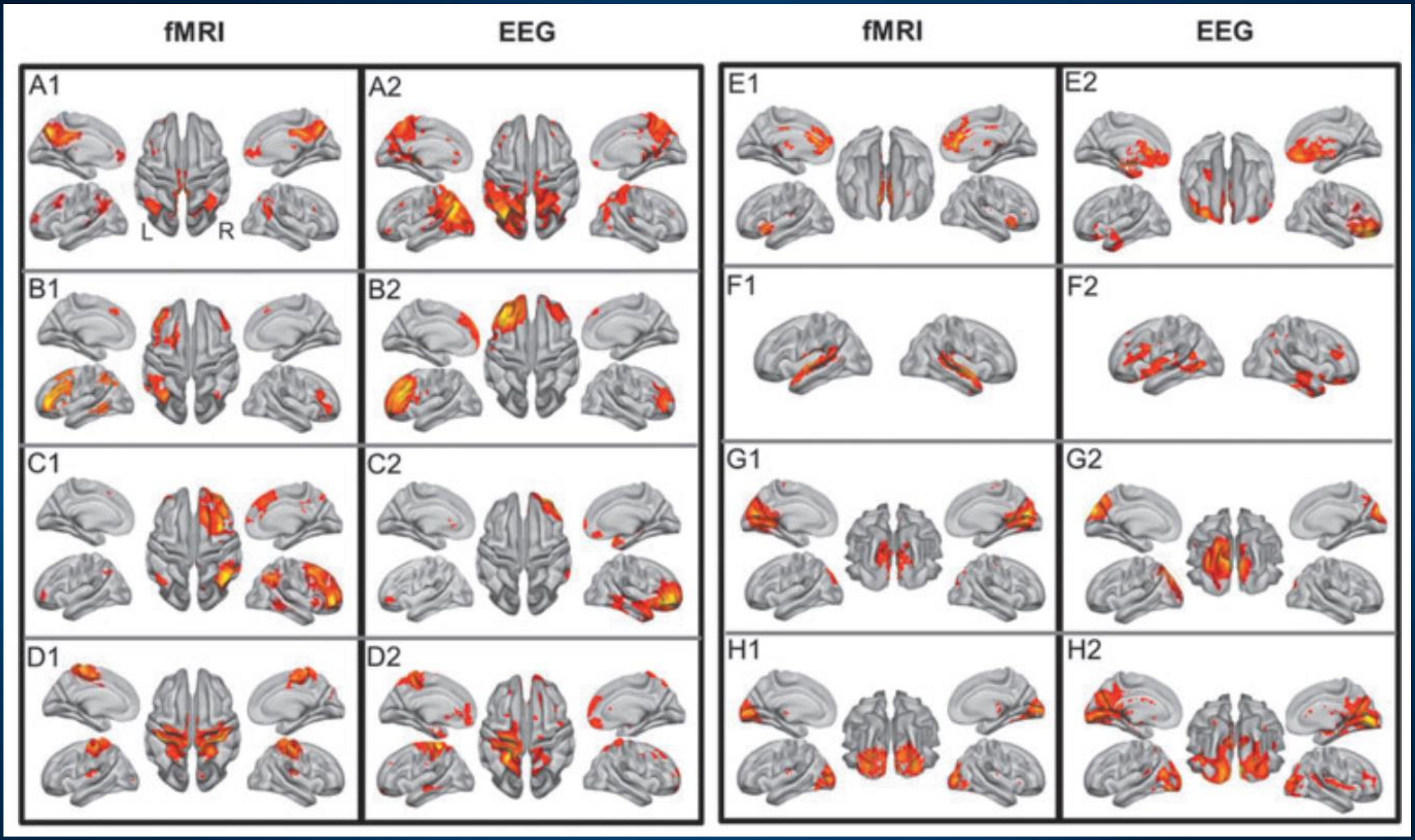
Category traffic light: Passive Viewing



Yuan .. Bodurka, 2015

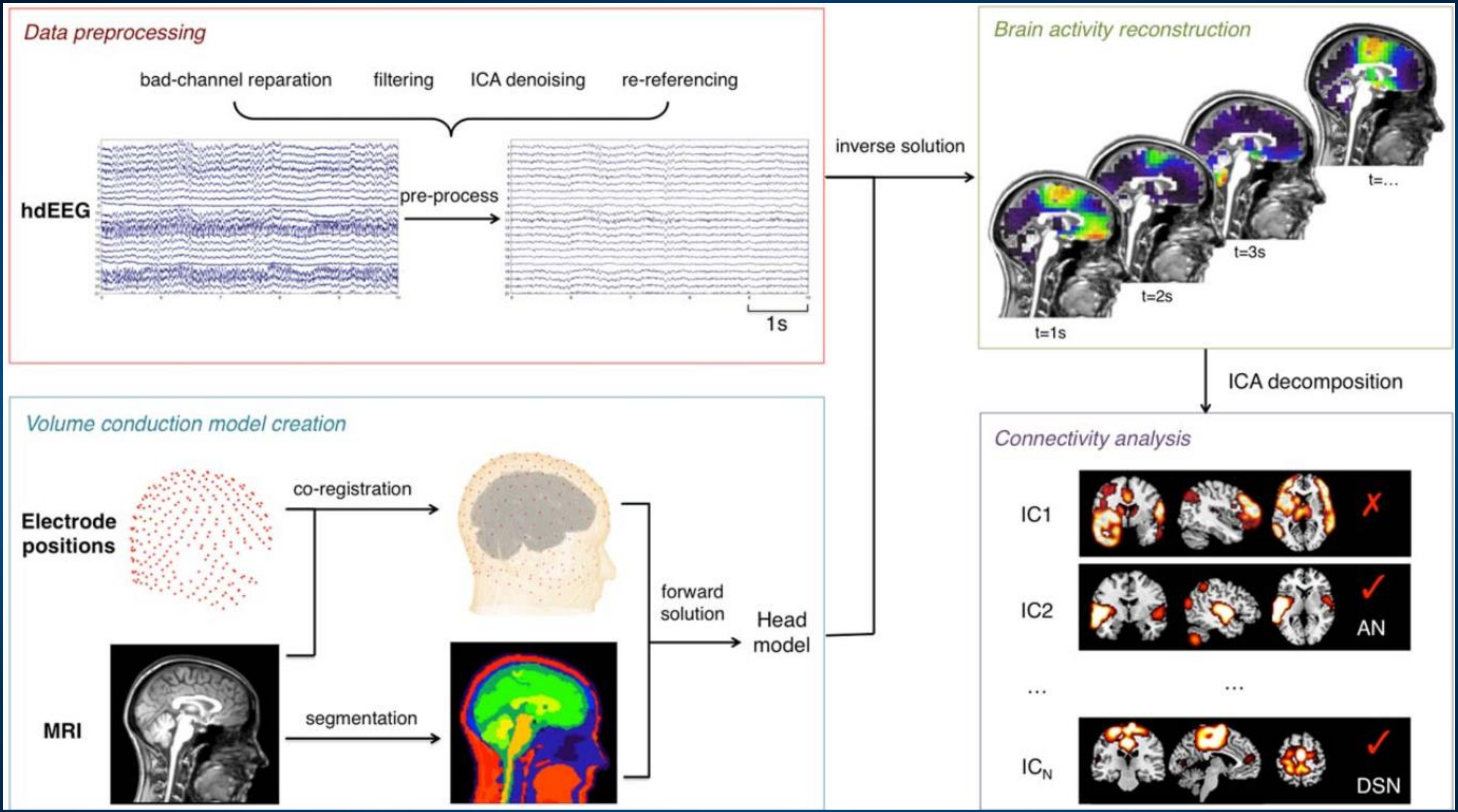


8 large networks from BOLD-EEG



DMN, FP (frontoparietal)-left, right, sensorimotor, ex, control, auditory, visual (medial), (H) visual (lateral).   Yuan … Bodurka (2015)

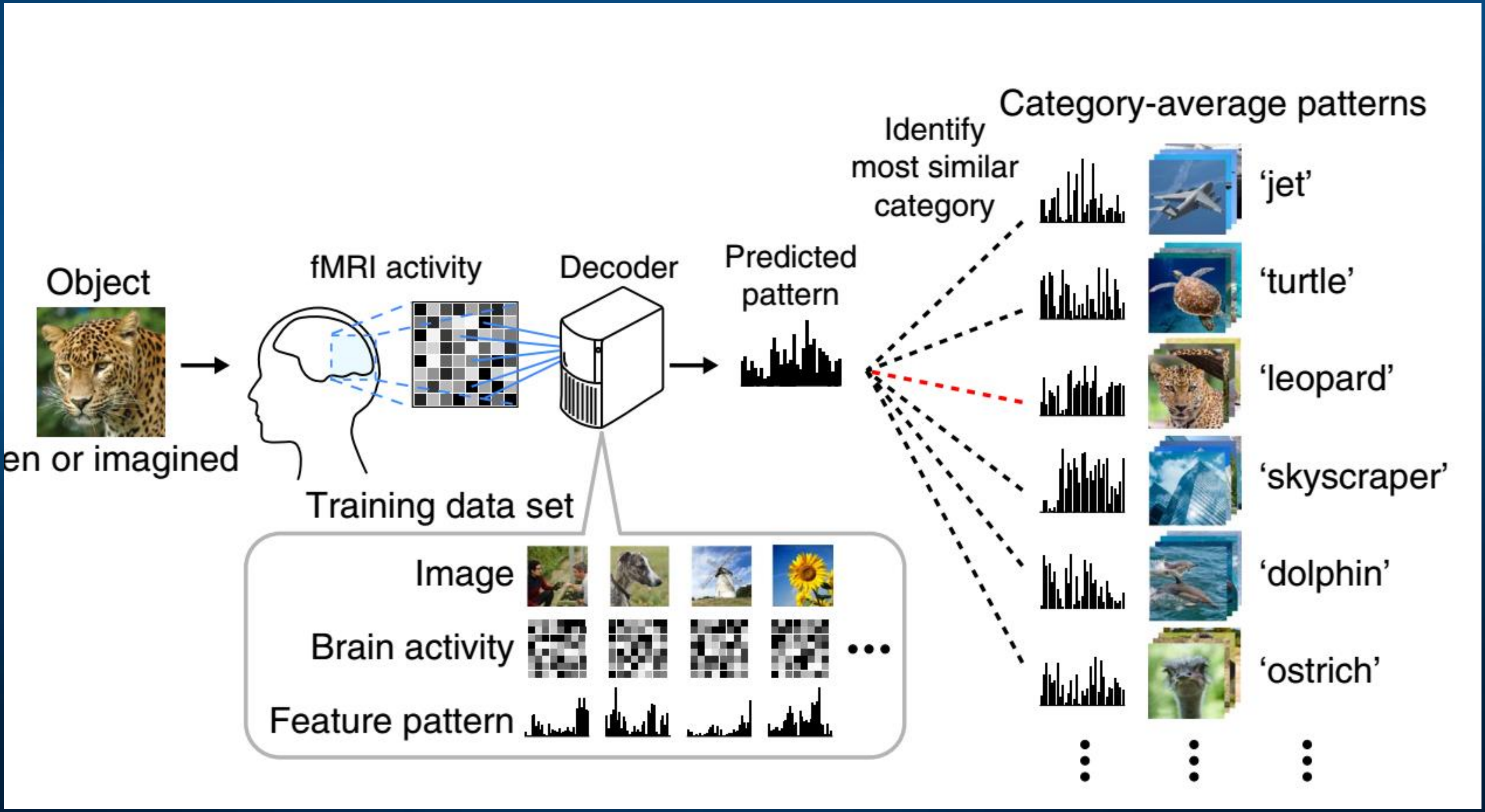
14 networks from BOLD-EEG



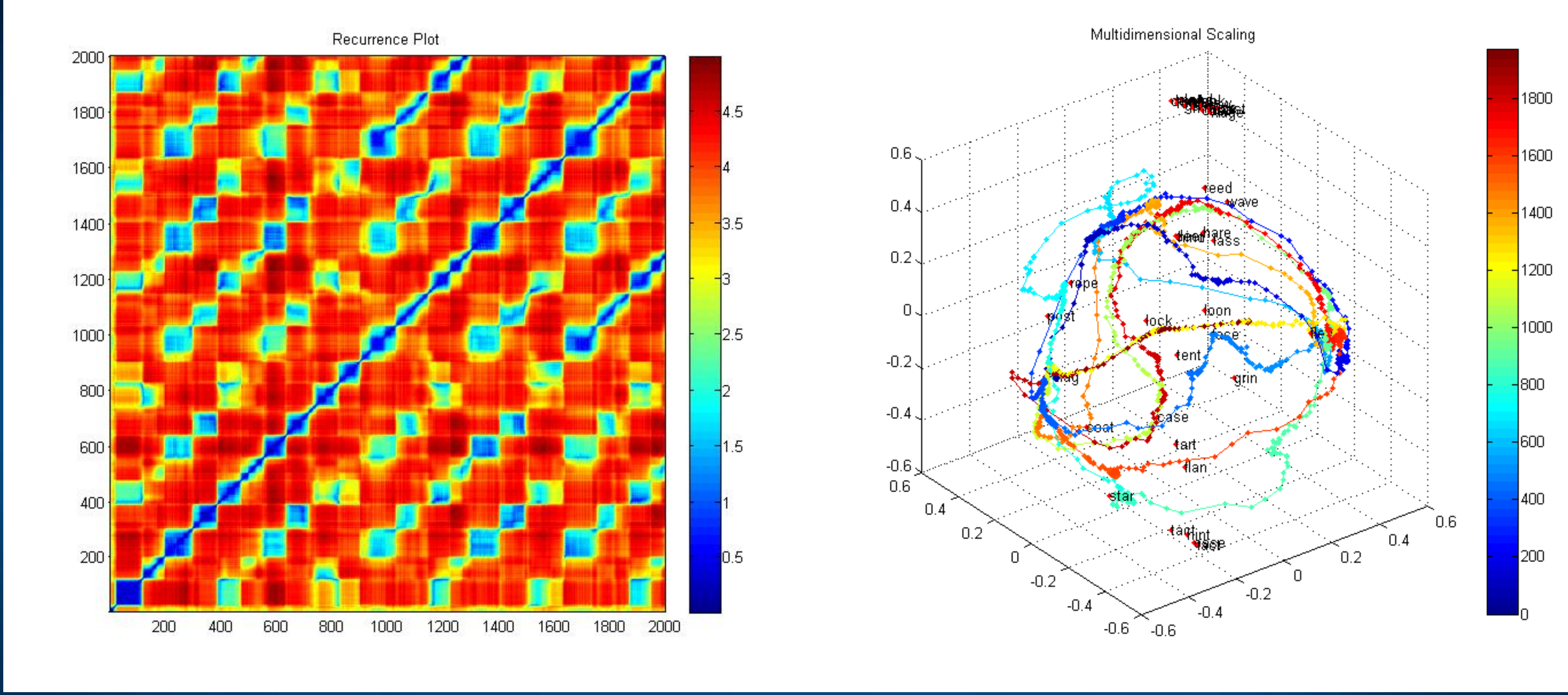
Liu et al. Detecting large-scale networks in the human brain. HBM (2017; 2018).

Brain activity ⇔ Mental image

fMRI activity can be correlated with deep CNN network features on **new images**; using these features closest image from large database is selected. Horikawa, Kamitani, Generic decoding of seen and imagined objects using hierarchical visual features. Nature Comm. 2017.



Trajectory visualization



Recurrence plots and MDS/FSD/SNE visualization of trajectories of the brain activity. Here data from 140-dim semantic layer activity during spontaneous associations in the 40-words microdomain, starting with the word "flag".

Our toolbox: http://fizyka.umk.pl/~kdobosz/visertoolbox/

EEG early ASD detection

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

EEG of 3 to 36-month old babies, 19 electrodes selected from 64 or 128.

Daubechies (DB4) wavelets transform EEG signal into 6 bands.

7 features from Recurrence Quantitative Analysis (RQA): RP entropy, recurrence rate, laminarity, repetition, max/mean line length, trapping time.

In addition sample entropy and Detrended Fluctuation Analysis was used.

Nonlinear features were computed from EEG signals and used as input to statistical learning methods. Prediction of the clinical diagnostic outcome of ASD or not ASD was highly accurate.

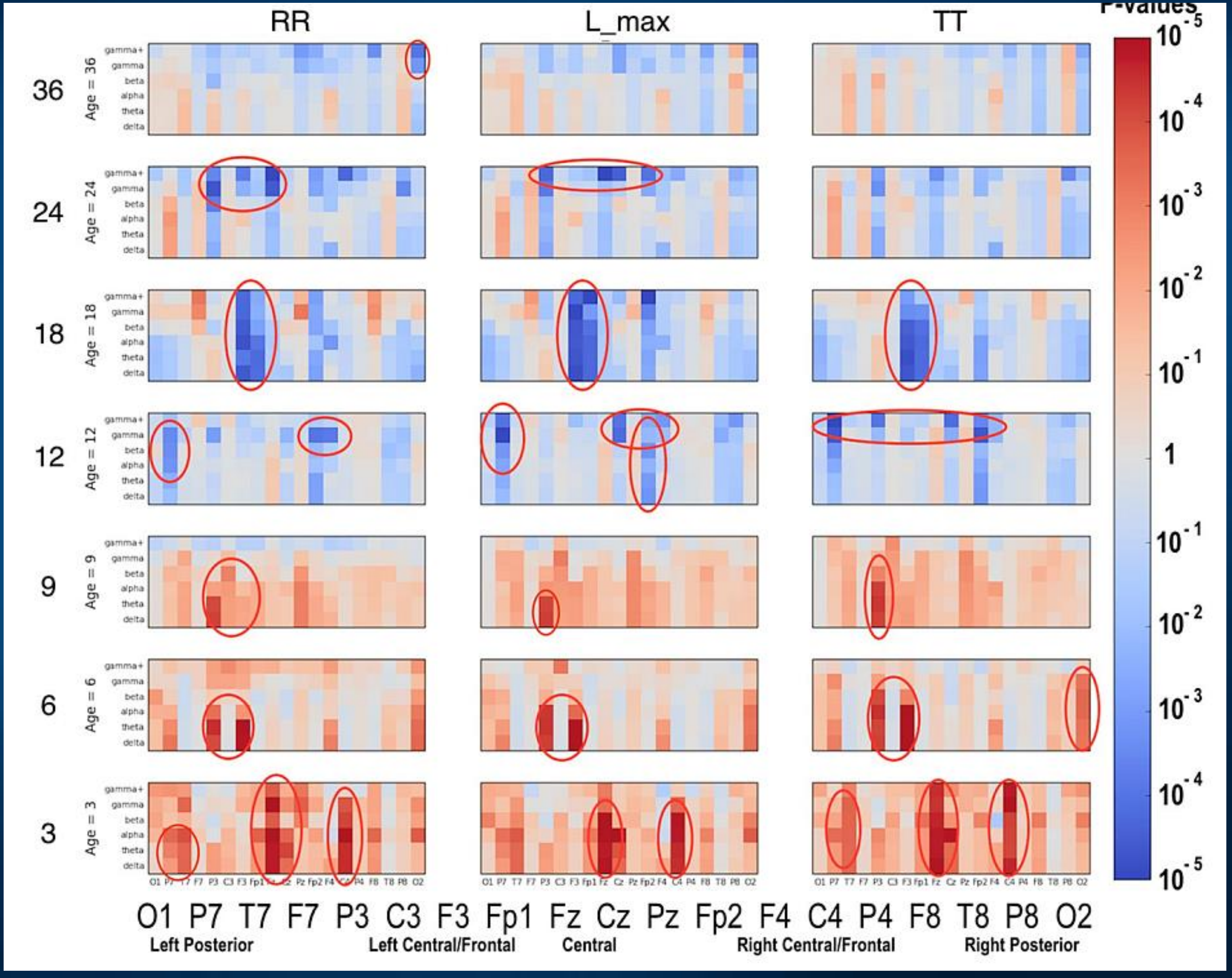
SVM classification with 9 features gave high specificity and sensitivity, exceeding 95% at some ages. Prediction using only EEG data taken as early as 3 months of age was strongly correlated with the actual measured scores.

ASD vs Low Risk Healthy

RR = recurrence rate

L_max = max line length, related to Lyapunov exponent

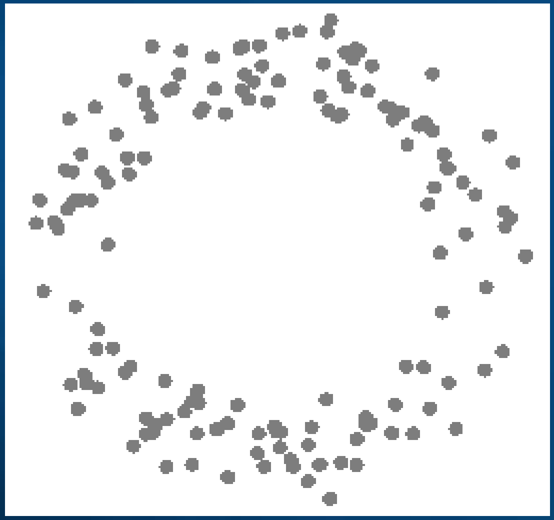
TT = trapping time

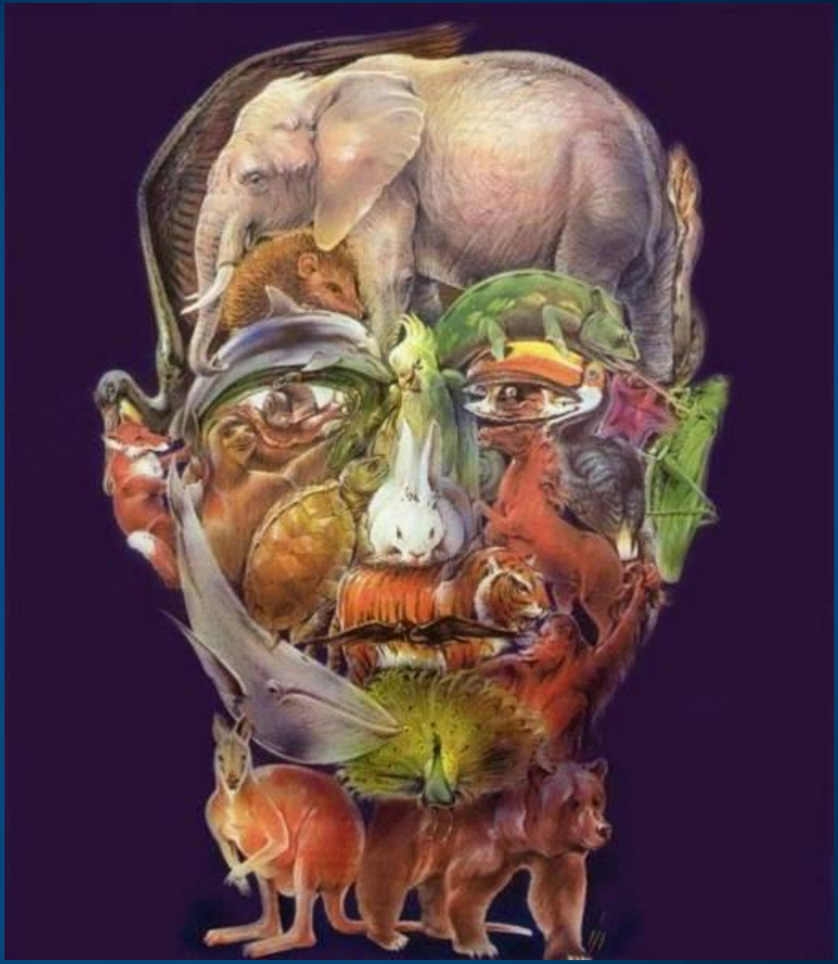


Perspectives

- Precise **diagnosis** of various subtypes of mental disorders - organic problems, schizophrenia, epilepsy, learning disabilities, depression, cognitive impairment (MCI), Alzheimer etc. -requires **good features** based on brain connectivity and functional large scale networks.
- **Closed loop neurofeedback for neurorehabilitation** after stroke, TBI, brain tumors, ASD, attention deficits, drug addiction, various forms of pain … Discovering deficits in information flow in the brain, targeting neuroplasticity in specific brain areas to form new functional connections.
- **Monitoring development** of children and infants, unfolding full developmental potential of children!
- **Disorders of consciousness** – better diagnosis and communication with patients in coma, MCS and VS.
- **Memory improvement** in MCI through neuromodulation and in future through deep brain stimulation.

Thank you for synchronization of your neurons





Google: W. Duch

=> talks, papers, lectures, Flipboard …