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Applications of High-order Interactions in Neuroscience

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HOI-BrainMod:
Workshop on Brain Modeling and High-Order Interactions
Amsterdam, May 7th, 2025
Institute for Advanced Studies

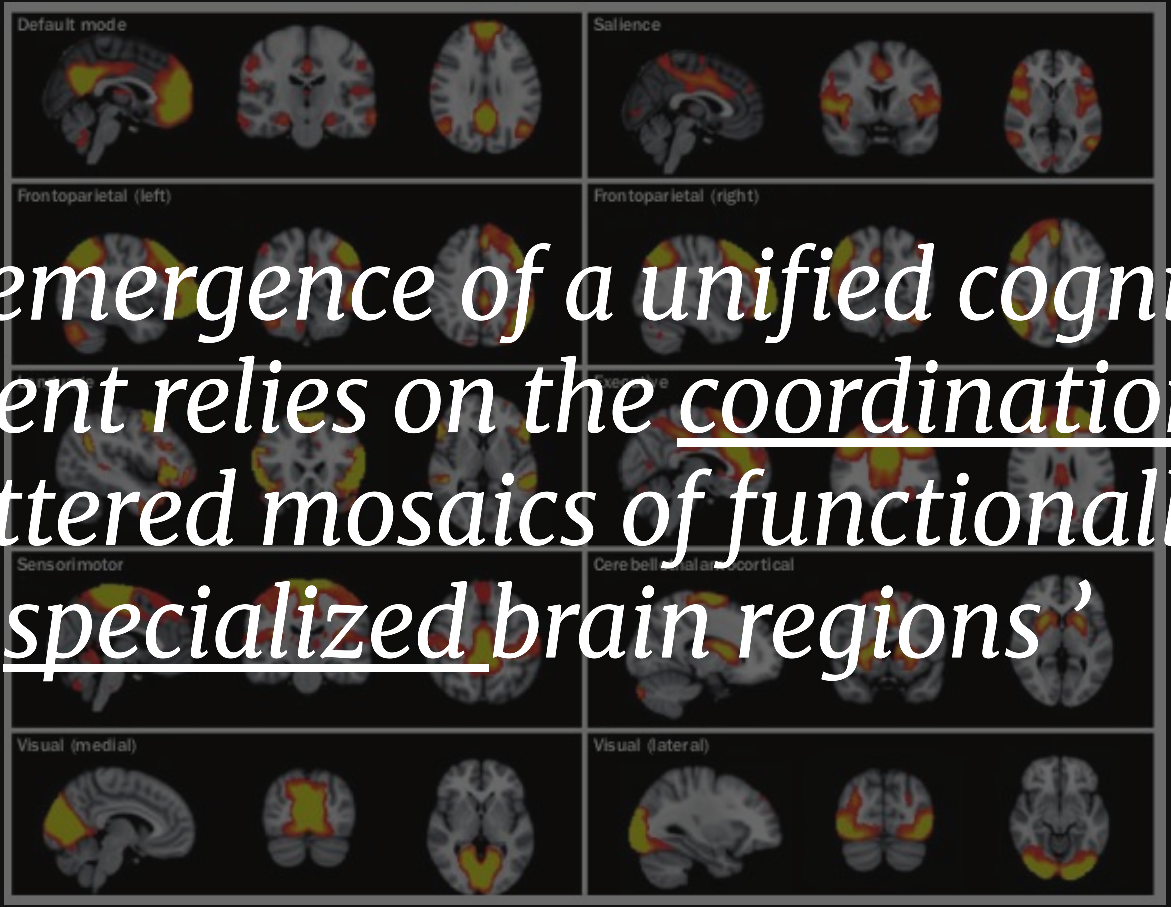
Outline

1. **<u>Motivation</u>**
   a. Complexity, integration and segregation in the brain
   b. Brain spatio temporal scale
   c. Flavors of integration

2. **<u>Methods:</u>**
   a. Estimators
   b. The combinatorial explosion
   c. Optimizations

3. **<u>Applications:</u>**
   a. Brain resting state: static and time varying synergy
   b. Healthy Aging
   c. Neurodegeneration
   d. States of consciousness

Motivation

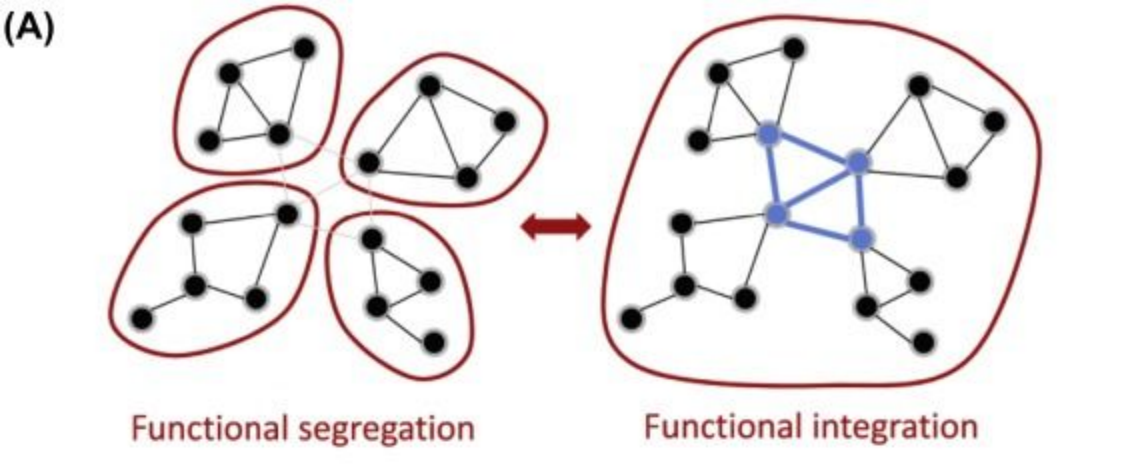


‘ The emergence of a unified cognitive moment relies on the coordination of scattered mosaics of functionally specialized brain regions ’

Varela, F., Lachaux, JP., Rodriguez, E. et al. 2001. **The brainweb: Phase synchronization and large-scale integration**. Nat Rev Neurosci.

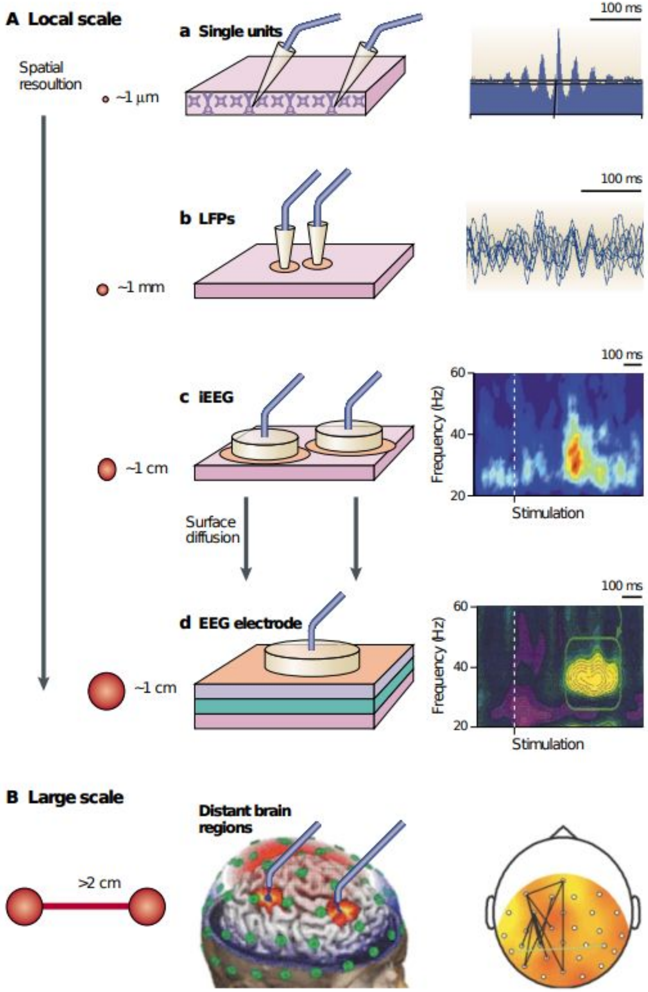
Pievani M, Filippini N, van den Heuvel MP, Cappa SF, Frisoni GB. 2014. **Brain connectivity in neurodegenerative diseases--from phenotype to proteinopathy**. Nat Rev Neurol.

Complexity, Integration and Segregation in the brain



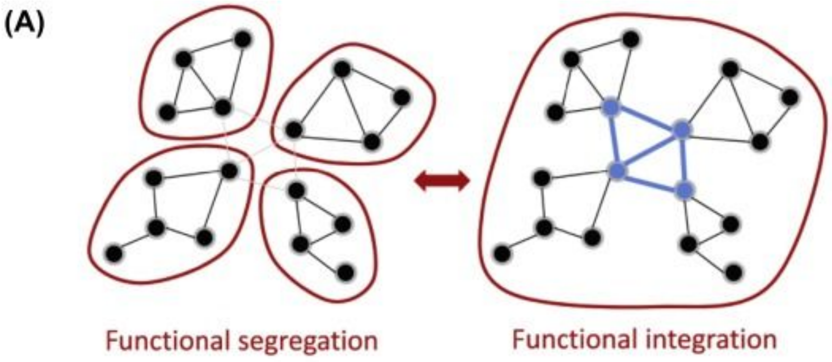
Shine 2019. **Neuromodulatory Influences on Integration and Segregation in the Brain**

Complexity: **coherent collective behaviour, non-linear, multi-order and multi-level dependencies**



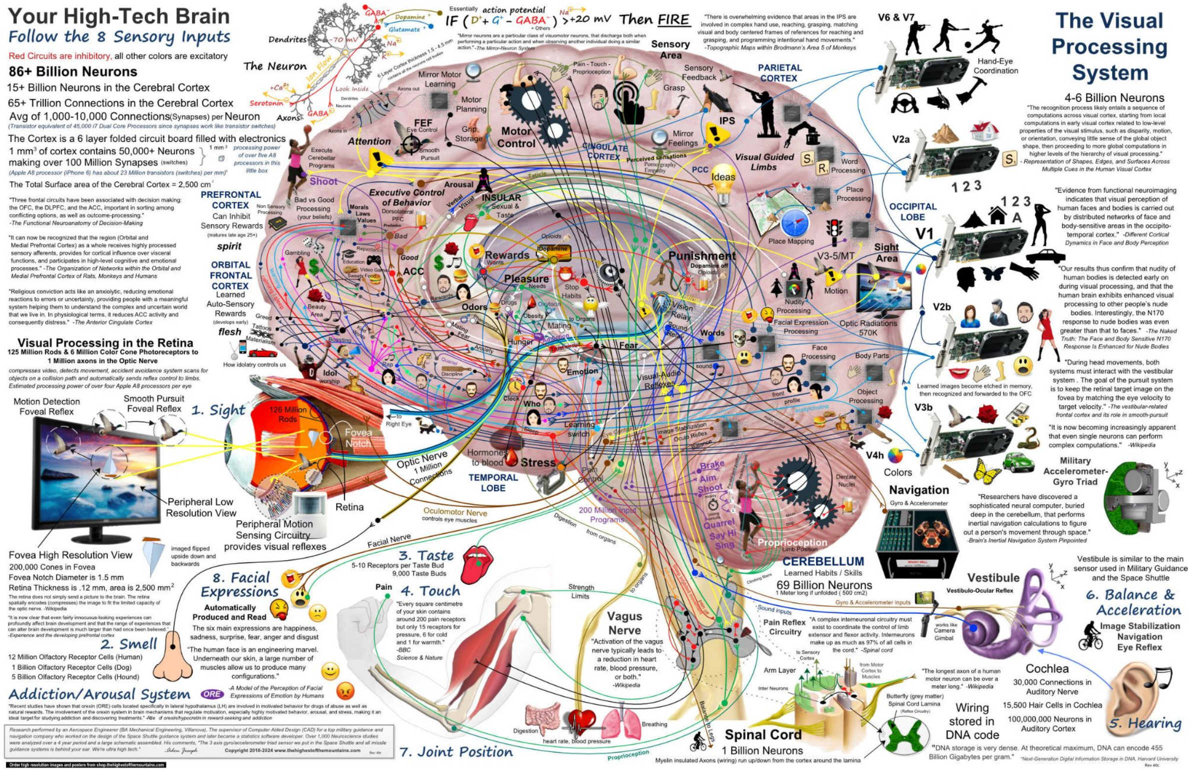
Varela, F., Lachaux, JP., Rodriguez, E. et al. 2001. **The brainweb: Phase synchronization and large-scale integration**. Nat Rev Neurosci.

- **Multiple statistical dependencies within and between spatio temporal scales**
- **Dependencies = Integration**
- **Information theory as a data-driven tool for measuring integration/segregation in the brain *within* and *between* scales.**



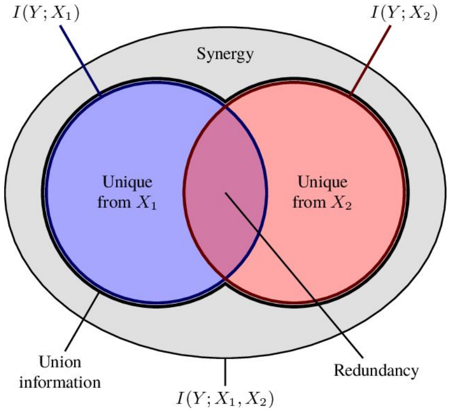
Shine 2019. **Neuromodulatory Influences on Integration and Segregation in the Brain**

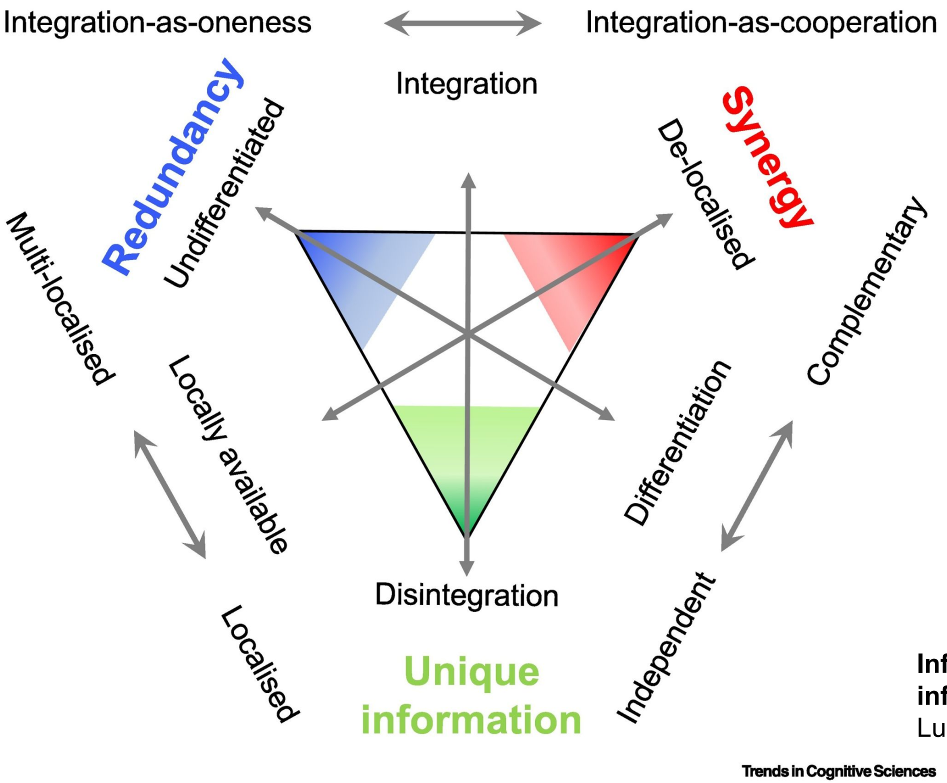
Cognition and Communication in the Brain



www.thehighestofthemountains.com

Flavors of Integration and Information Decomposition



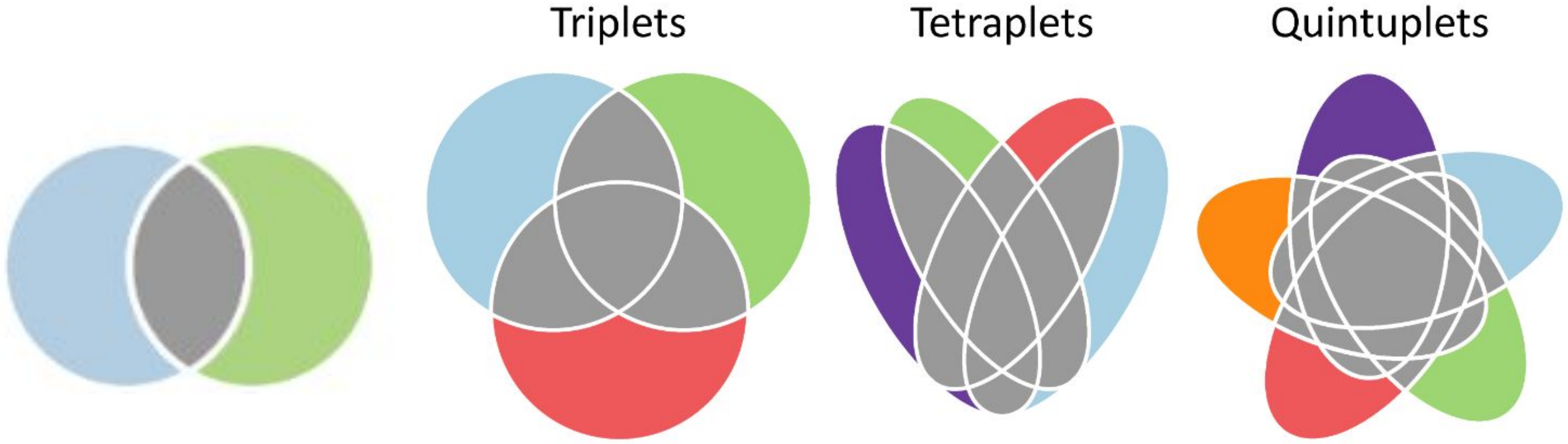


Information decomposition and the informational architecture of the brain. Luppi et al. 2024.

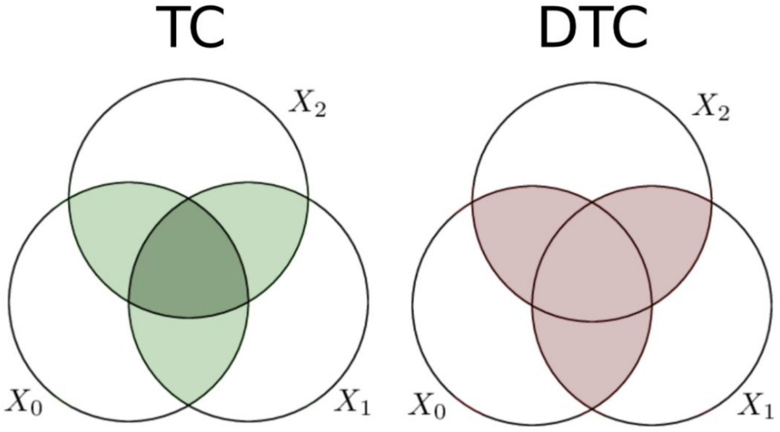
Methods

- Estimators
- The Combinatorial Explosion of High-Order Interactions
- Strategies and Optimizations

Generalization of the Mutual Information for Higher-Orders



Information Decomposition: Quantifying high-order dependencies



Fernando E. Rosas, Pedro A. M. Mediano, Michael Gastpar, and Henrik J. Jensen. **Quantifying high-order interdependencies via multivariate extensions of the mutual information.** 2019. Phys. Rev. E.

$I(X_1, X_2) =$
$H(X_1) + H(X_2) - H(X_1, X_2) =$
$H(X_1, X_2) - H(X_1|X_2) - H(X_2|X_1)$

A. Total Correlation

$$TC(X^n) = \sum_{j=1}^{n} H(X_j) - H(X^n)$$

B. Dual Total Correlation

$$DTC(X^n) = H(X^n) - \sum_{j=1}^{n} H(X_j|X^n_{-j})$$

Information Decomposition: Quantifying high-order dependencies

O-Information (Ω) F. Rosas, P. Mediano 2019, Physical Review E

$$\Omega_n(X_1, \ldots, X_n) = TC - DTC =$$
$$(n-2)H(X_1, \ldots, X_n) + \sum_{j=1}^{n}[H(X_j) - H(X_1, \ldots, X_{j-1}, X_{j+1}, \ldots, X_n)]$$

Dominance

$$\Omega_n(X_1, \ldots, X_n) > 0: \text{ Redundancy,}$$
$$\Omega_n(X_1, \ldots, X_n) < 0: \text{ Synergy}$$

S-Information: Overarching correlations

$$\mathrm{S}_n(X_1, \ldots, X_n) = TC + DTC$$

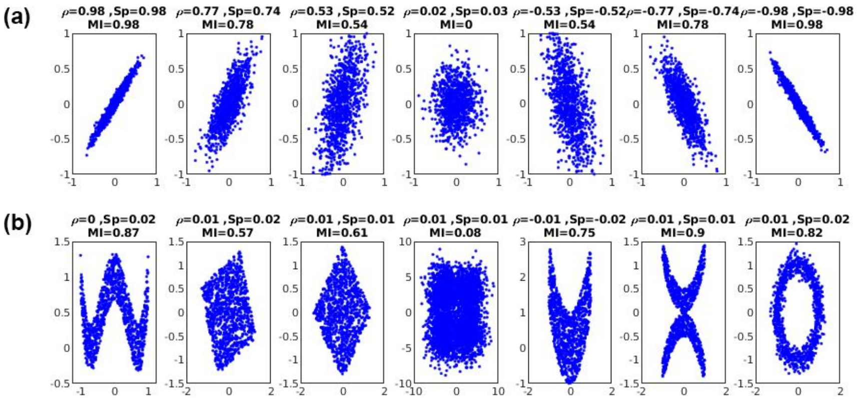
Characterising high-order interdependence via entropic conjugation. Rosas et al. 2024. arXiv

Estimating (joint) Differential Entropy for Continuous Variables

<u>**All of the measures can be expressed as a sum of low and high-order entropies.**</u>

(***Characterising high-order interdependence via entropic conjugation***. *Rosas et al. 2024. arXiv*)

- **Histogram**
  - Uses arbitrary bins
- **Assuming a specific distribution (e.g. Gaussian)**
  - Data may not be Gaussian
- **Gaussian Copula Approach**
  - May overlook higher-order moments of the distribution
- **Elliptical Distributions (Hindriks et al. 2025)**
- **Non-parametric**
  - Kernel based
  - Nearest neighbors (Kozachenko-Leonenko)



The Combinatorial Explosion of High-Order Interactions

$$\sum_{k=0}^{n} \binom{n}{k} = 2^n$$

$$\binom{n}{0} + \binom{n}{1} + \binom{n}{2} + \sum_{k=3}^{n} \binom{n}{k} = 2^n$$

$$\sum_{k=3}^{n} \binom{n}{k} = 2^n - 1 - n - \frac{n(n-1)}{2}$$

Exponential growth
For a moderate sized network e.g. n=30 variables,
the number of interactions grows up to 10^9

The Combinatorial Explosion: Strategies and Optimizations

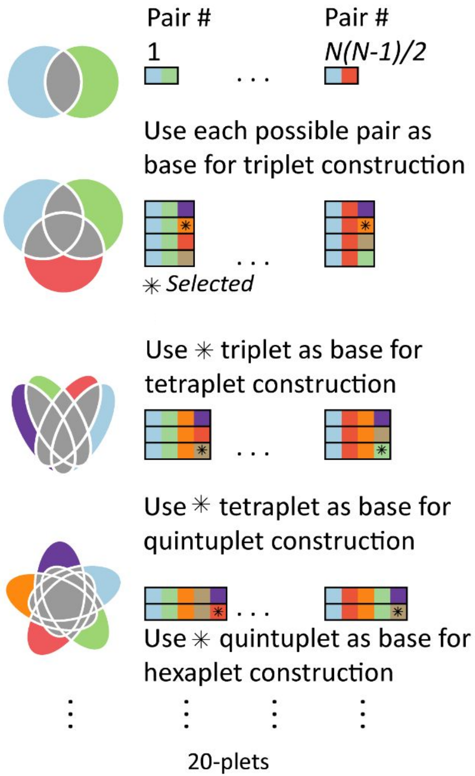
- **Exhaustive**
  - Typically infeasible for n>25.
- **Random search**
  - May overlook relevant interactions.
- **Greedy Algorithm**
  - Deterministic: Optimization based on local solutions.
- **Simulated Annealing**
  - Stochastic: Perturbs local solutions to escape local minima.
- **Gradient Descent**
  - Not known implementation, but O-information Gradients have been defined (Scagliarini et al 2022).

THOI Tutorial

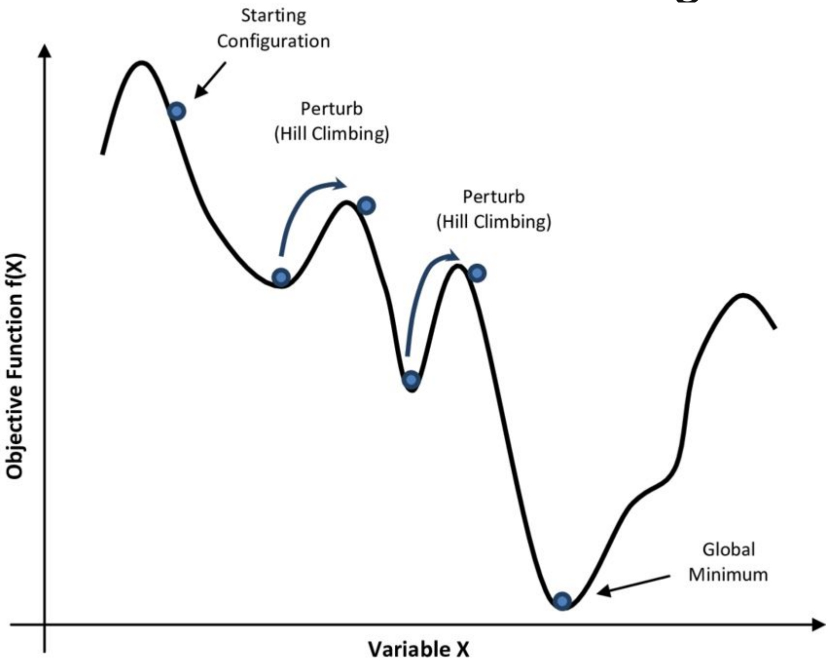
Optimizations

Searching for the interaction that optimizes a given measure

Greedy



Simulated Annealing



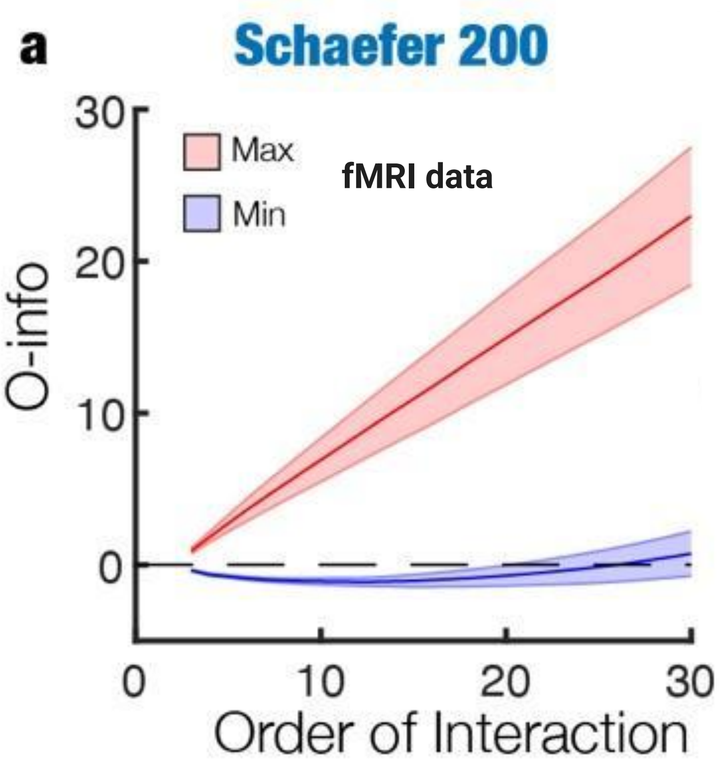
The free parameters are the indices of the variables

Example Output of Optimizing the O-information

<u>Maximizing O-information:</u>
Interactions dominated by redundancy
Maximal integration-as-oneness

<u>Minimizing O-information:</u>
Interactions dominated by synergy
Maximal integration-as-cooperation

Can coexists *within* and *across* orders of interaction



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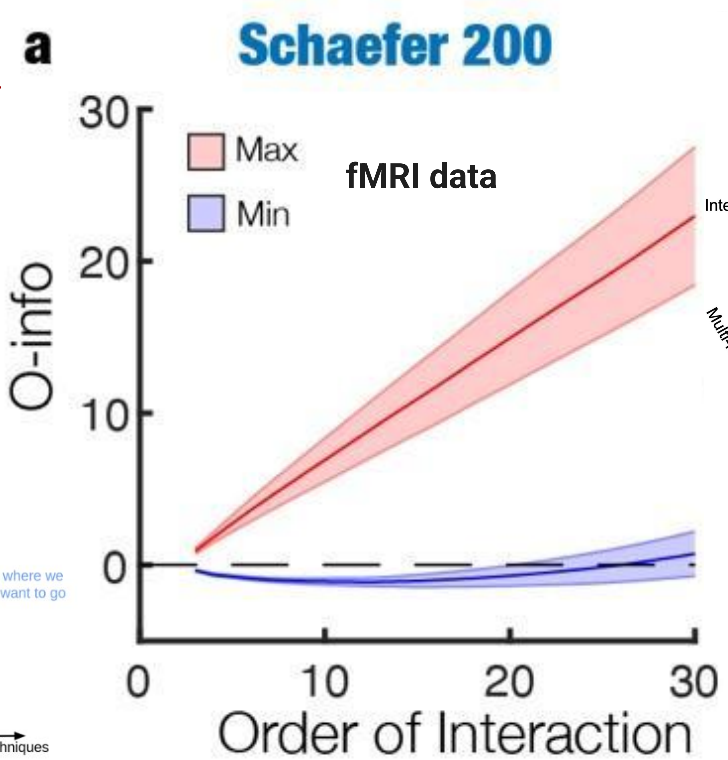
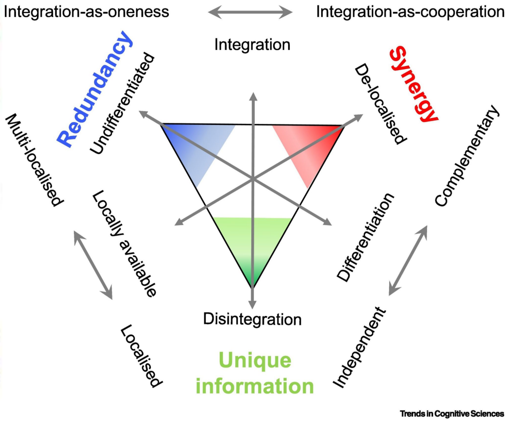
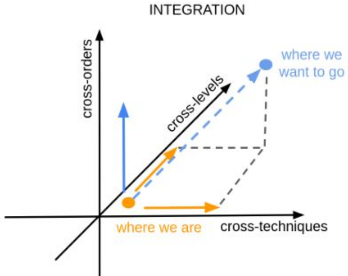






Open Source Toolboxes for Continuous Data

- **JIDT** (https://jlizier.github.io/jidt/)
  - Java-based. Implements many estimators.
- **HOI** (https://brainets.github.io/hoi/)
  - Python. Implements many estimators.

- **THOI** (https://github.com/Laouen/THOI)
  - Python. Exploits the Gaussian approach for efficient batch processing.
  - Designed for dealing with the combinatorial explosion
    Tutorial!!

High-order Applications

Not this type of ‘High’-order…

Applications

a. Brain resting state

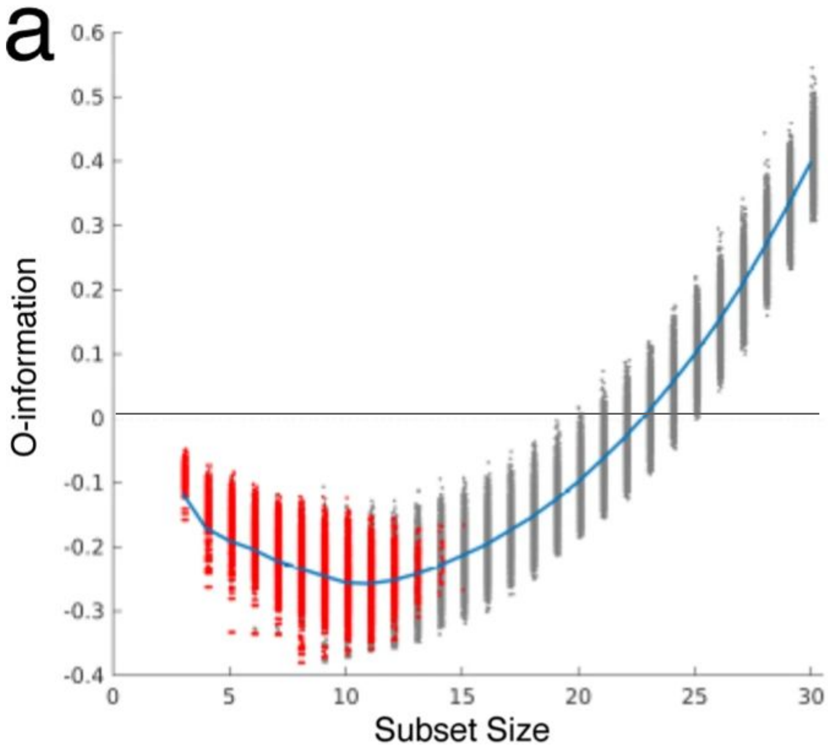
b. Healthy Aging

c. Neurodegeneration

d. States of consciousness

Resting State fMRI

The ‘resting’ brain exhibits synergistics interactions



nature › communications biology › articles › article

Article | Open access | Published: 24 April 2023

Multivariate information theory uncovers synergistic subsystems of the human cerebral cortex

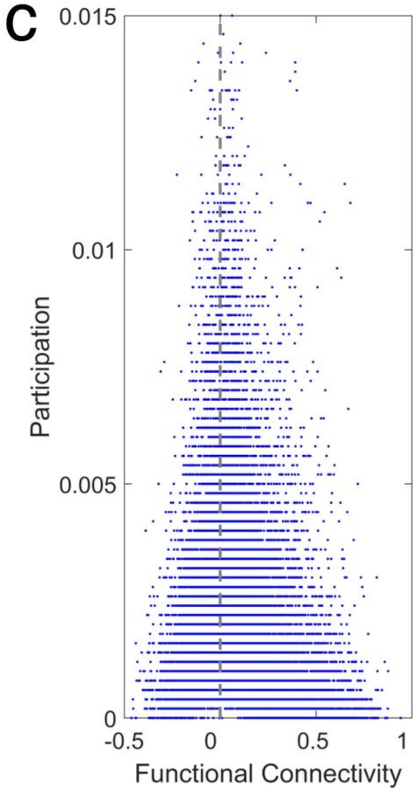
Thomas F. Varley, Maria Pope, Joshua Faskowitz & Olaf Sporns

Communications Biology **6**, Article number: 451 (2023) | Cite this article

6683 Accesses | **18** Citations | **25** Altmetric | Metrics

Schaeffer 200 using Simulated annealing

The 'resting' brain exhibits synergistics interactions



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Participation of pairs of nodes in synergistic 10-plets

Node pairs that are more frequently encountered in synergistic interactions tend to show weak FC

Emergence of high-order functional hubs

New Results

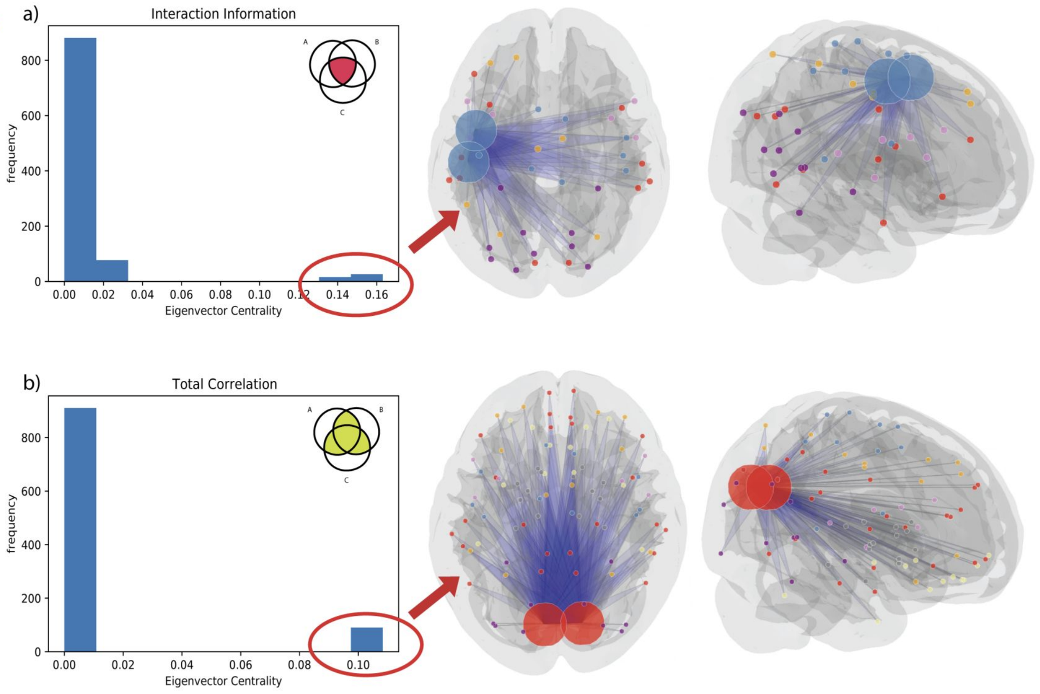
Follow this preprint

Emergence of High-Order Functional Hubs in the Human Brain

Fernando A.N. Santos, Prejaas K.B. Tewarie, Pierre Baudot, Antonio Luchicchi, Danillo Barros de Souza, Guillaume Girier, Ana P. Milan, Tommy Broeders, Eduarda G.Z. Centeno, Rodrigo Cofre, Fernando E Rosas, Davide Carone, James Kennedy, Cornelis J. Stam, Arjan Hillebrand, Mathieu Desroches, Serafim Rodrigues, Menno Schoonheim, Linda Douw, Rick Quax

doi: https://doi.org/10.1101/2023.02.10.528083

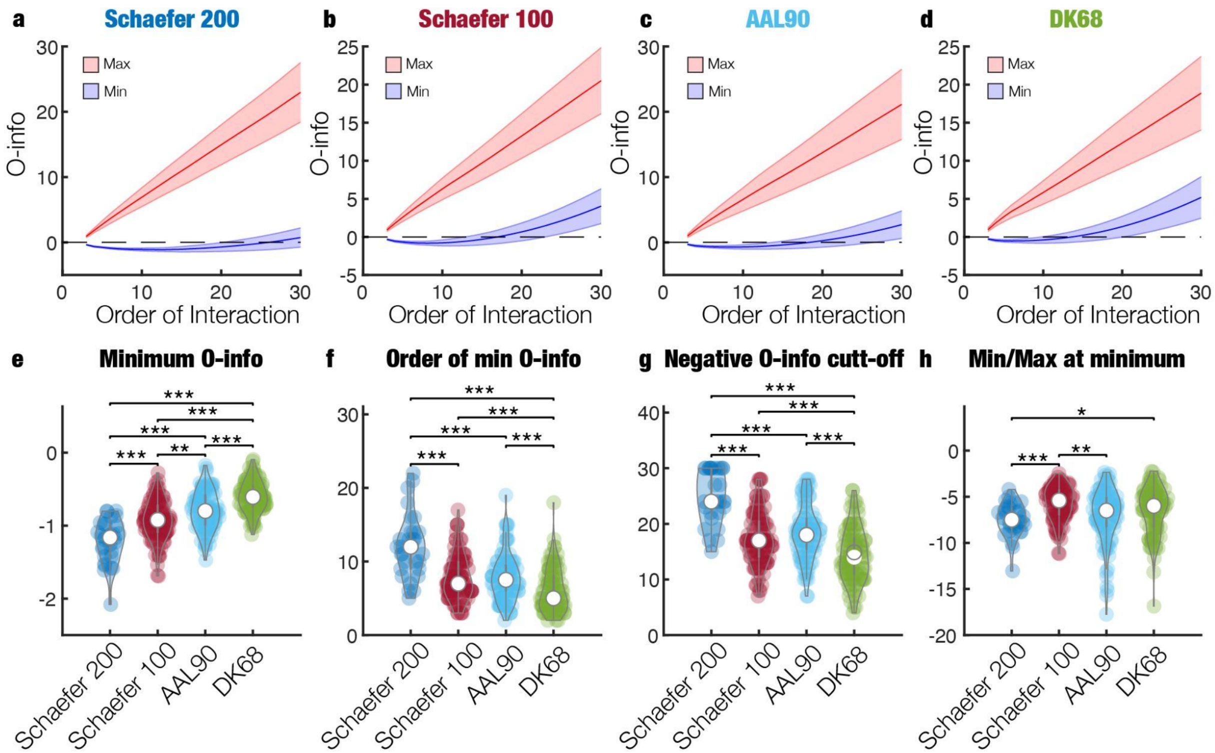
This article is a preprint and has not been certified by peer review [what does this mean?].



Synergy-related hubs are more integration-related (DMN and subcortex)

Redundancy (TC)-related hus are more segregation-related (visual and sensory-motor)

Synergistic interactions as function of coarse-graining



Greedy Approach

Synergistic interactions are confined to low to mid orders of interactions (<N/3).

Coarse-graining (parcellation) impacts the extent of synergistic interactions.

The synergistic interaction of low-dimensional brain modes
Herzog et al., *In Preparation*

Time-varying high-order interactions in the resting brain

Journal of Physics:
Complexity

PAPER • OPEN ACCESS

Time-varying synergy/redundancy dominance in the human cerebral cortex

To cite this article: Maria Pope *et al* 2025 *J. Phys. Complex.* **6** 015015

Using local entropies.
For ***x*** a single time points

$$h(x) = -\log p(x)$$

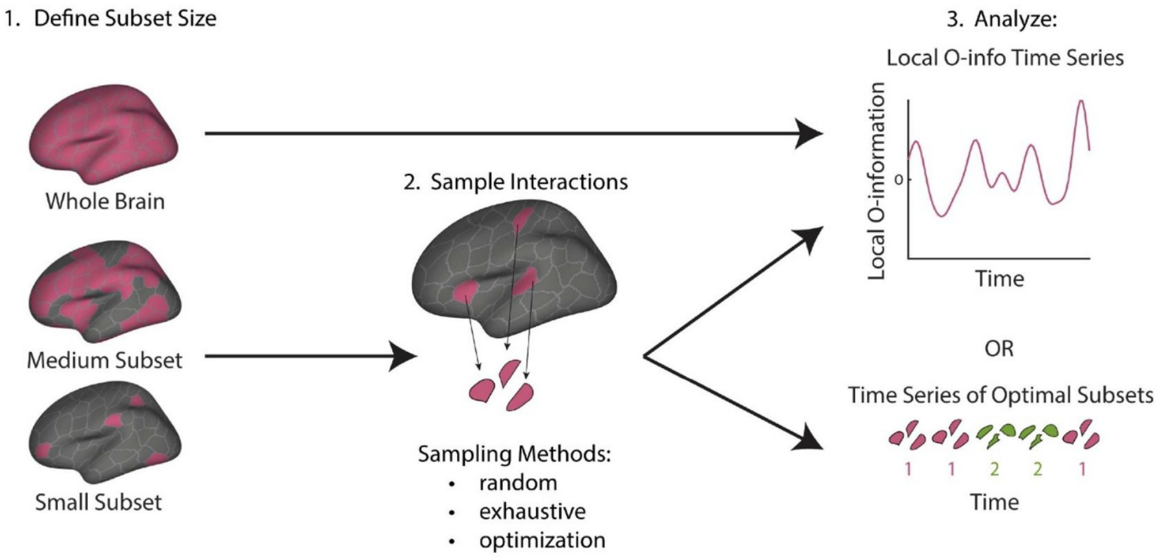


Figure 2. Schematic of approach. Analysis begins by choosing the size of interaction to be considered. If the interaction size is less than that of the whole brain, interactions are sampled either randomly, exhaustively, or by optimization. Finally, the resulting time series of the local O-information or the resulting time series of optimal subsets is analyzed to demonstrate relation to time-averaged metrics, recurrent and autocorrelated dynamics, and relation to node-level activity.

Time-varying high-order interactions in the resting brain

Journal of Physics: Complexity

PAPER • OPEN ACCESS

Time-varying synergy/redundancy dominance in the human cerebral cortex

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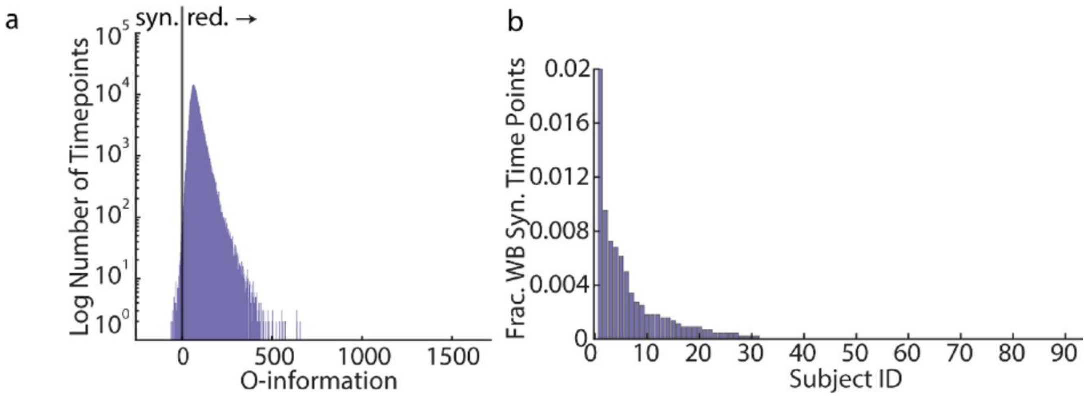
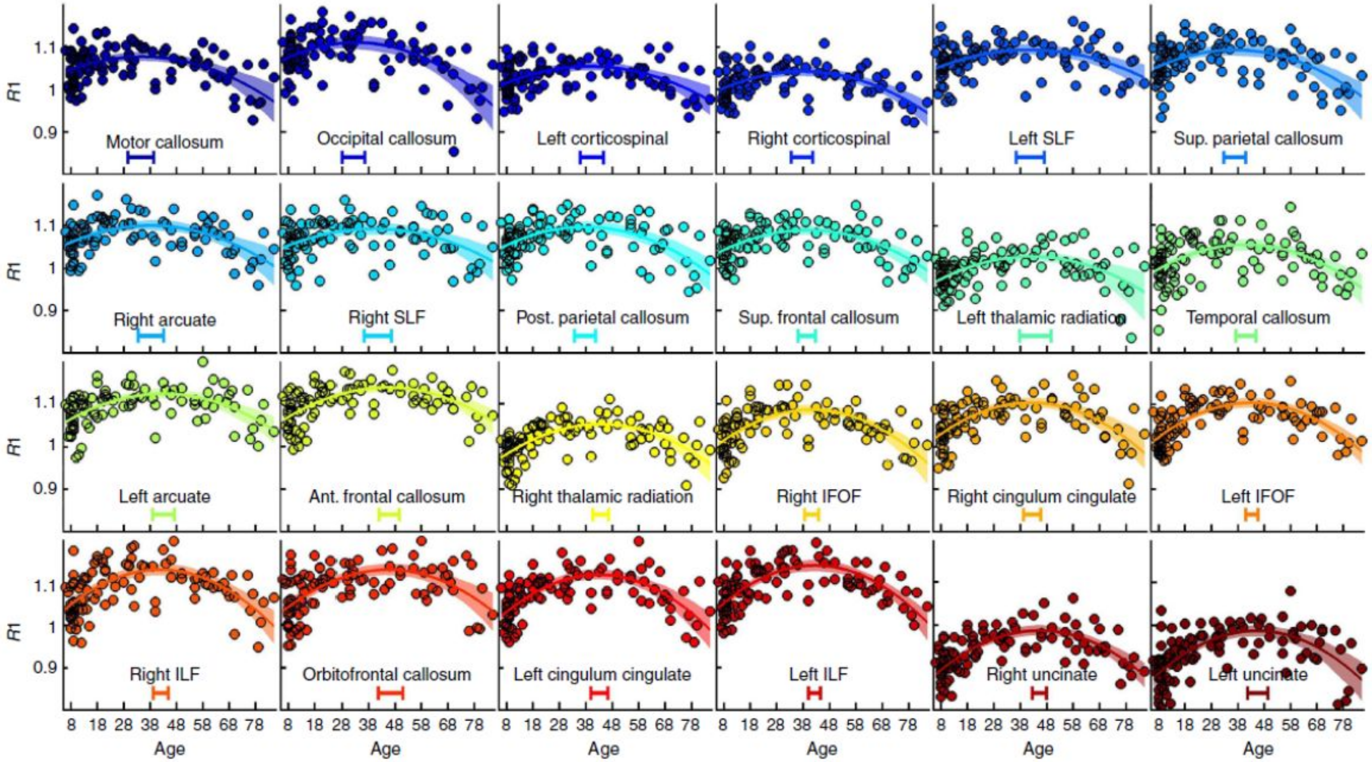
Whole-brain O-info



The whole-brain is rarely synergy-dominated

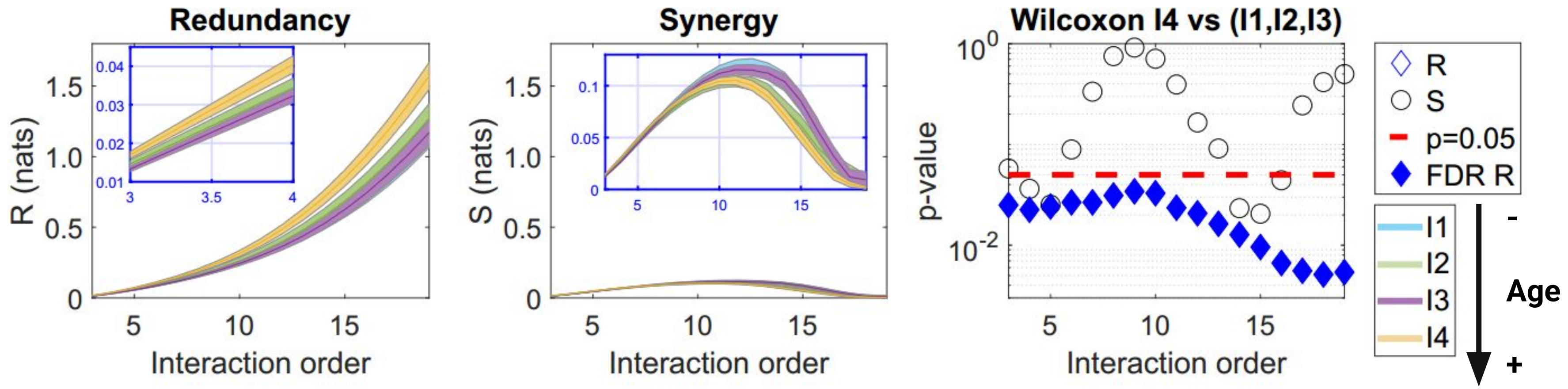
Healthy aging

Inverted U-shape of white matter



Yeatman 2014, Nature Communications

Healthy aging: changes in redundancy



The older participants exhibited a higher redundancy as compared to younger participants.

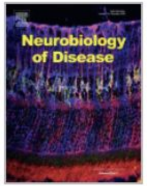
Gatica, et. al, 2021, Brain Connectivity

Neurodegeneration: Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD)

ELSEVIER

Neurobiology of Disease

Volume 175, December 2022, 105918



Genuine high-order interactions in brain networks and neurodegeneration

Rubén Herzog [a b], Fernando E. Rosas [b c d e f], Robert Whelan [g], Sol Fittipaldi [a g i], Hernando Santamaria-Garcia [a], Josephine Cruzat [a b], Agustina Birba [i], Sebastian Moguilner [a], Enzo Tagliazucchi [a h], Pavel Prado [a], Agustin Ibanez [a g i j]

Disruption of brain networks in neurodegeneration

__Disruptions in structural and functional connectivity__

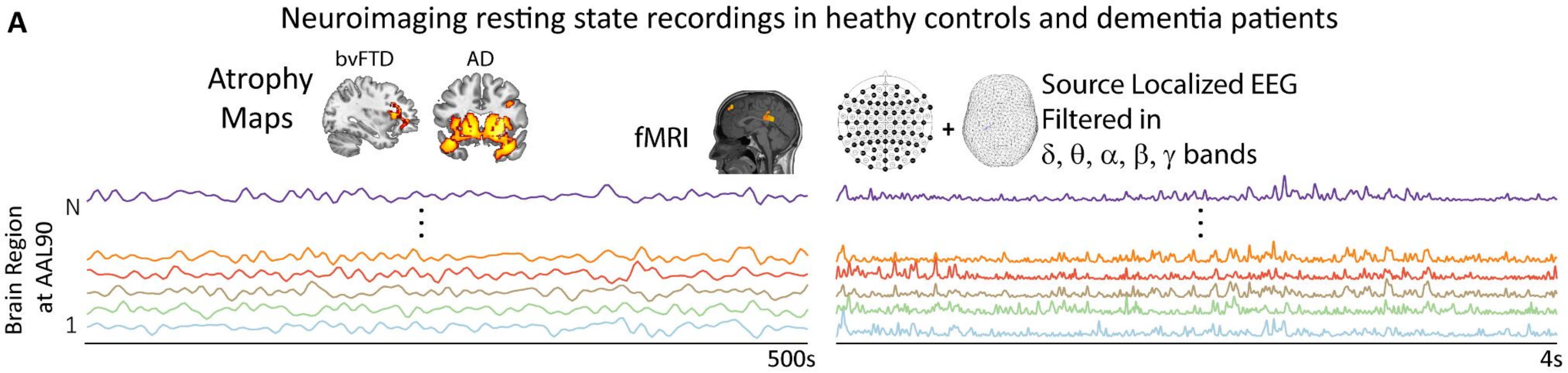
Table 1 | Connectivity correlates of clinical phenotypes

Clinical phenotype	Network	Connectivity changes	Correlation with symptom severity	Changes track disease stage*	Changes track disease progression‡	Connectivity changes in other networks
Functional connectivity						
AD[29–35,42,43]	DMN	↓↓↓	+++	+++	+	↓/↑
bvFTD[35,42,44,49]	Salience	↓↓	++	NA	NA	↓/↑
PSP[50,51]	Cerebellothalamocortical	↓↓	++	NA	NA	↓
ALS[56–61,76–78]	Sensorimotor	↓/↑	+/–	NA	NA	↓/↑
PD[79–87,90]	Cerebellothalamocortical	↓/↑	+/–	NA	NA	↓
HD[91–94]	Sensorimotor	↓/↑	+/–	NA	NA	↓/↑
Structural connectivity						
AD[37–41]	Limbic	↓↓↓	+++	++	+	↓↓↓
bvFTD[41,45–48]	Frontal	↓↓↓	+++	NA	NA	↓↓↓
PSP[51,53–55]	Cerebellothalamocortical	↓↓↓	+/–	NA	NA	↓↓↓
ALS[60–77]	Sensorimotor	↓↓↓	+++	NA	+++	↓↓
PD[88,89]	Cerebellothalamocortical	↓↓	++	++	NA	↓↓
HD[95–100]	Sensorimotor	↓↓↓	+++	+++	NA	↓↓↓

*Cross-sectional studies. ‡Longitudinal studies. Evidence from cross-sectional and longitudinal studies indicates that functional connectivity biomarkers are associated with the clinical phenotype and disease severity in AD and bvFTD. These biomarkers seem to be specific to the clinical phenotype. In PSP, the evidence is similar but still preliminary. In ALS, PD and HD, no functional connectivity signature was consistently identified. Structural connectivity biomarkers are strongly associated with clinical phenotype and disease severity in all neurodegenerative diseases. Key: ↓, reduced connectivity; ↑, increased connectivity; +, yes; –, no; +++, ↓↓↓, consistent evidence from multiple studies; ++, ↓↓, overall consistent evidence from multiple studies; +, ↓, evidence from single study; +/–, ↓/↑, conflicting evidence. Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioural variant frontotemporal dementia; CST, corticospinal tract; HD, Huntington disease; NA, not assessed; PD, Parkinson disease; PSP, progressive supranuclear palsy.

Pievani M, Filippini N, van den Heuvel MP, Cappa SF, Frisoni GB. 2014. **Brain connectivity in neurodegenerative diseases--from phenotype to proteinopathy**. Nat Rev Neurol.

Multimodal resting state recordings of patients and healthy controls using EEG and fMRI

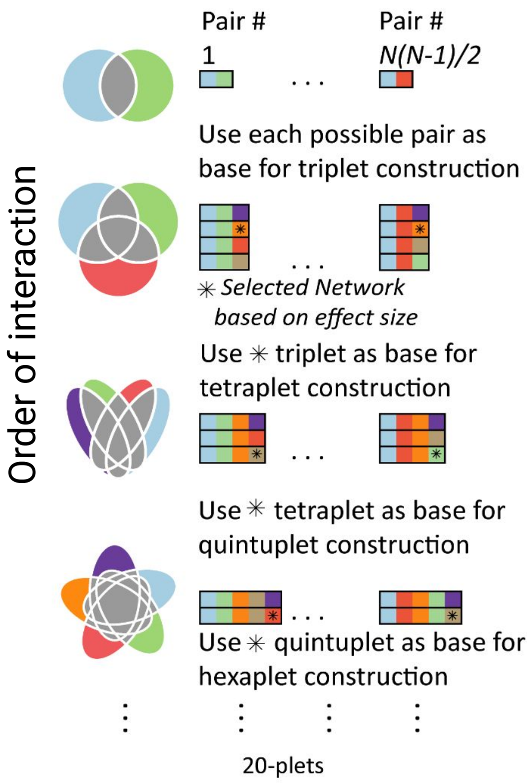


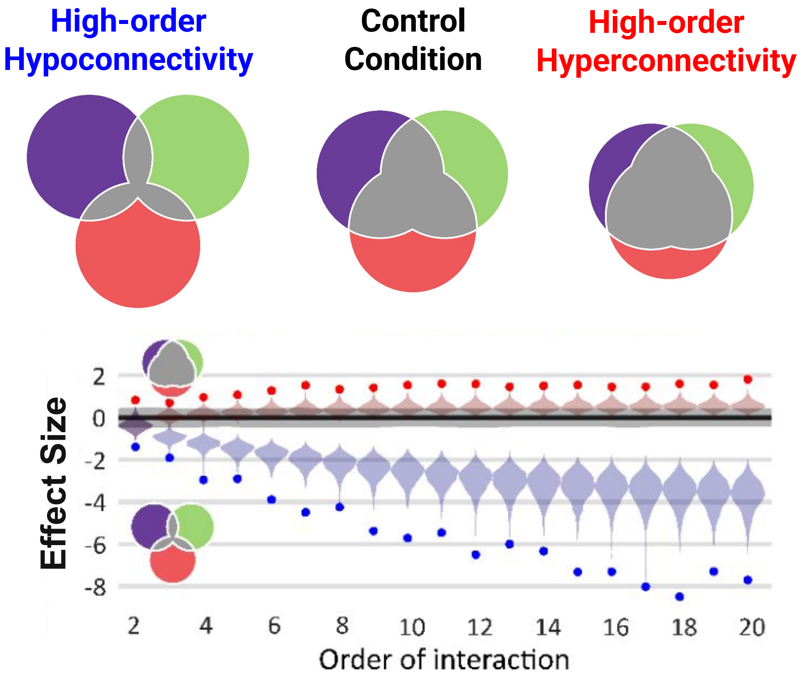
5-7 mins of resting state high-density EEG and fMRI (separate) recordings of healthy controls (**CN,** **N=95**), patients with Alzheimer's disease (**AD,** **N=49**), and behavioral variant of frontotemporal dementia (**bvFTD, N=45**).

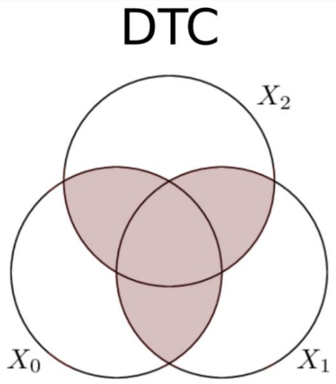
ReD-Lat
Multi-Partner Consortium to Expand Dementia Research in Latin America

Searching for changes between conditions

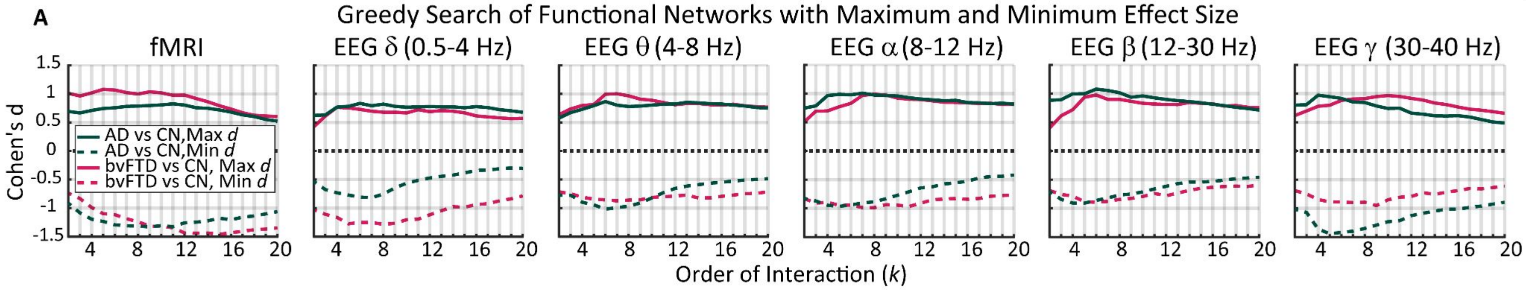
DTC-based Greedy Search of Most Compromised Networks

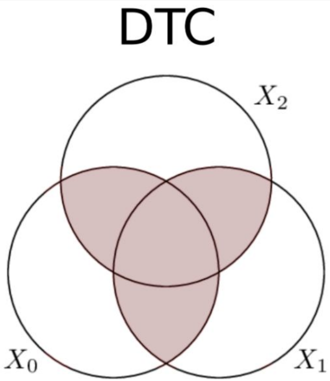




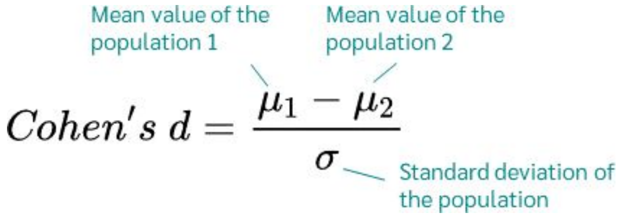


Neurodegeneration disrupts brain HOIs in multiple spatiotemporal scales



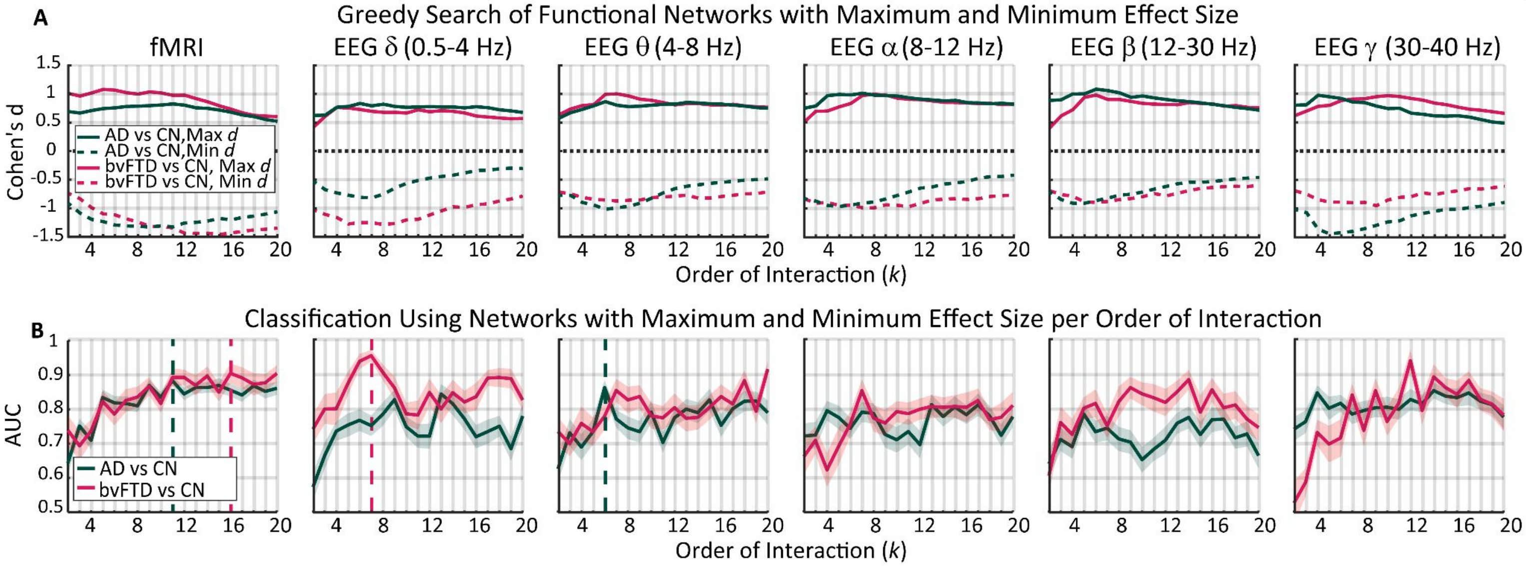


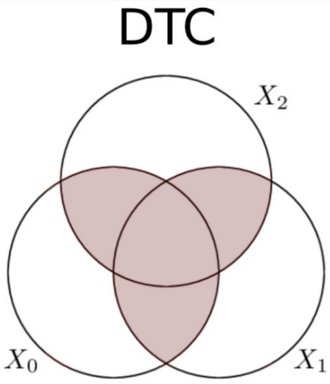
- Optimization of the *effect size* on the DTC for each order of interaction.



$$Cohen's\ d = \frac{\mu_1 - \mu_2}{\sigma}$$

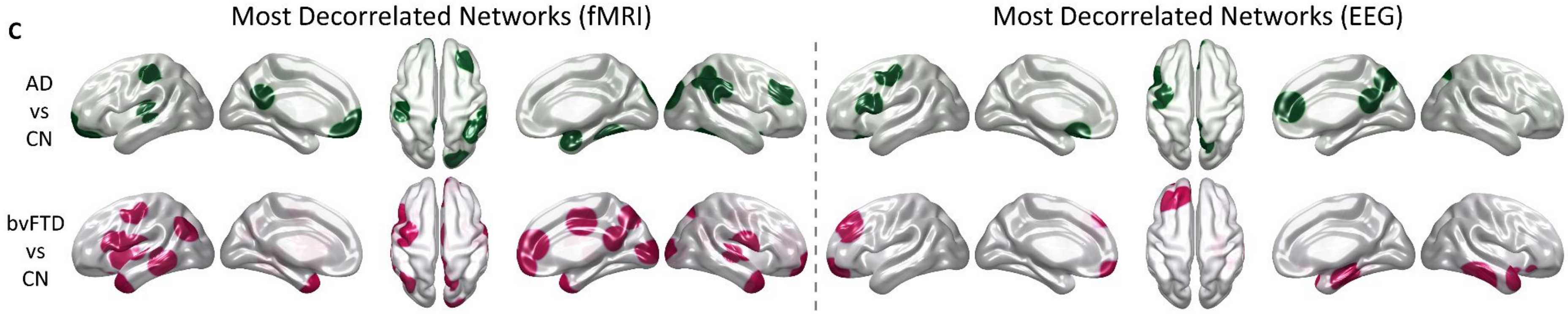
Neurodegeneration disrupts brain HOIs in multiple spatiotemporal scales





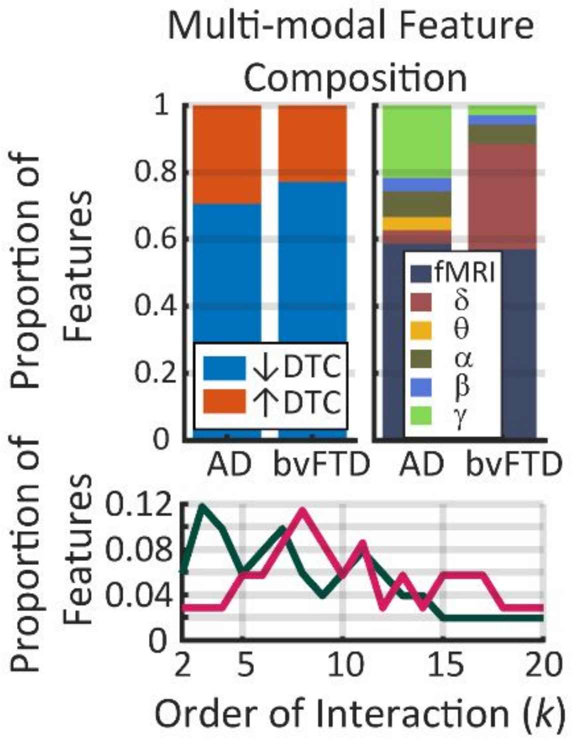
- Using the HOI with maximum and minimum effect size per order to classify the conditions with a Random Forest

Neurodegeneration disrupts brain HOIs in multiple spatiotemporal scales



fMRI and EEG revealed different disrupted brain high-order interactions

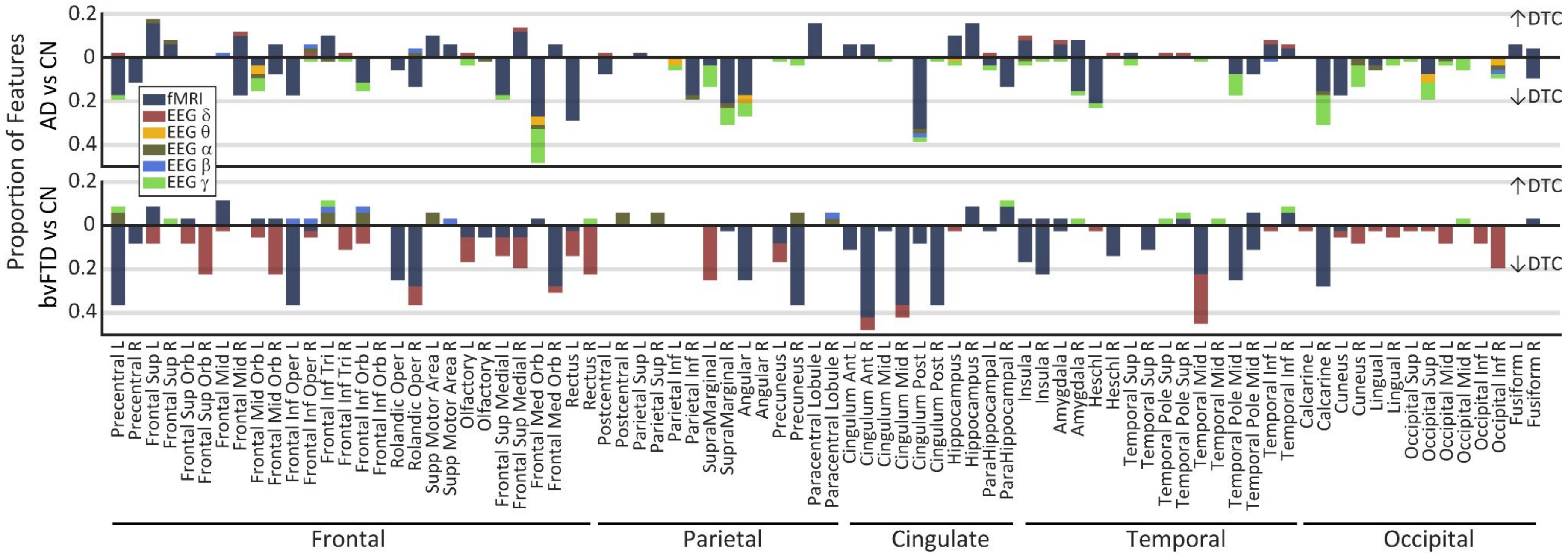
Multimodal integration reveals that Dementia is dominated by high-order hypoconnectivity



Selection of most relevant HOIs by feature selection

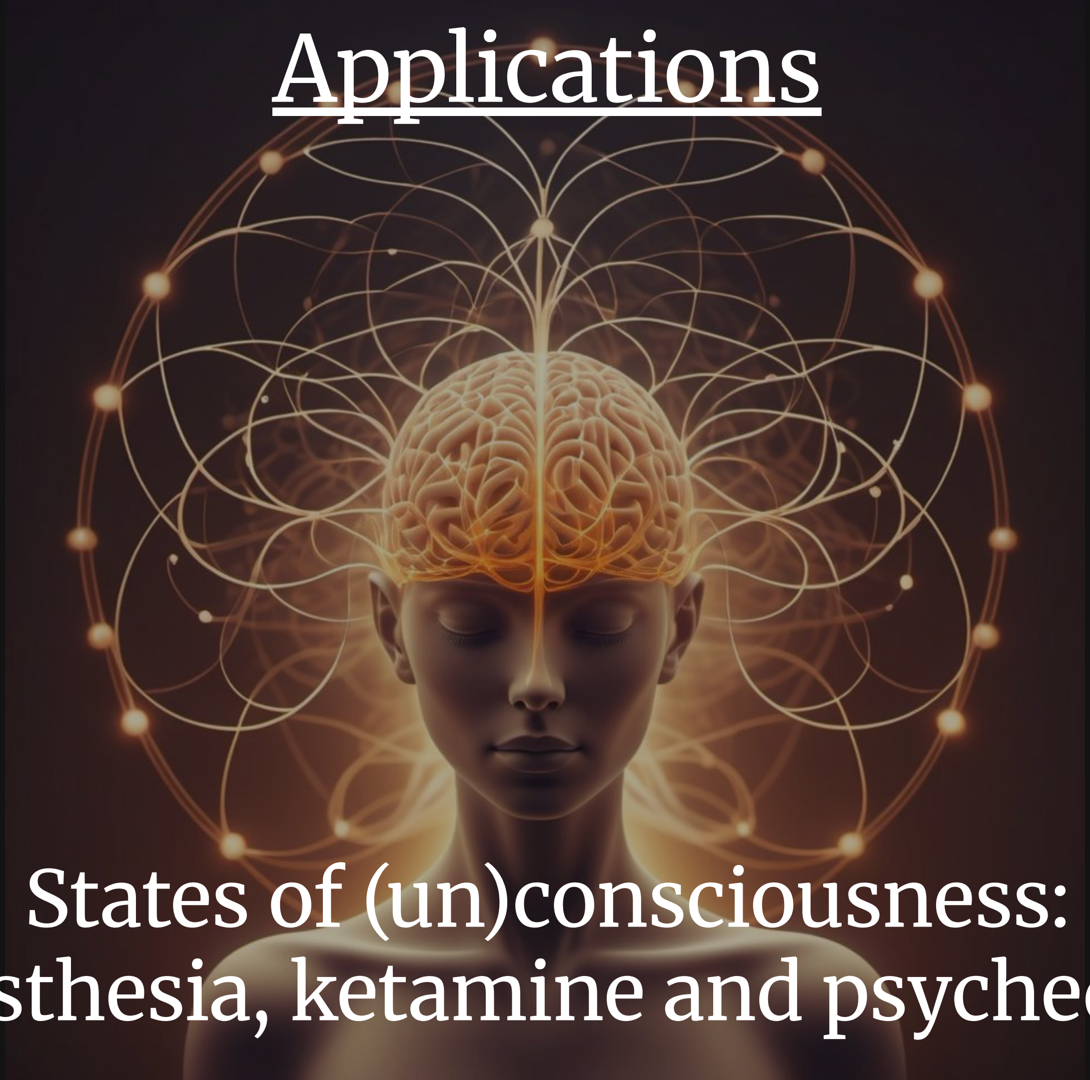
- N Features: AD=51, bvFTD=35
- Hypoconnectivity > Hyperconnectivity
- Larger contribution of **fMRI** than EEG
- Disease-specific contribution of EEG frequency bands
- Larger networks in bvFTD than AD

Specific pathophysiological signatures of neurodegeneration revealed by multimodal data



Specific pathophysiological signatures of neurodegeneration revealed by multimodal data

Applications



States of (un)consciousness:
Anaesthesia, ketamine and psychedelics

Consciousness and brain complexity

nature > communications biology > articles > article

Article | Open access | Published: 15 December 2022

Neural complexity is a common denominator of human consciousness across diverse regimes of cortical dynamics

Joel Frohlich, Jeffrey N. Chiang, Pedro A. M. Mediano, Mark Nespeca, Vidya Saravanapandian, Daniel Toker, John Dell'Italia, Joerg F. Hipp, Shafali S. Jeste, Catherine J. Chu, Lynne M. Bird & Martin M. Monti

Communications Biology **5**, Article number: 1374 (2022) | Cite this article

JOURNAL ARTICLE

Consciousness and complexity: a consilience of evidence

Simone Sarasso, Adenauer Girardi Casali, Silvia Casarotto, Mario Rosanova, Corrado Sinigaglia, Marcello Massimini Author Notes

Neuroscience of Consciousness, Volume 2021, Issue 2, 2021, niab023, https://doi.org/10.1093/nc/niab023

Published: 30 August 2021 **Article history**

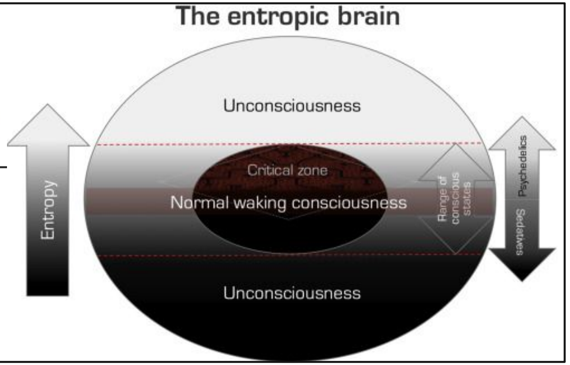
ELSEVIER

Neuropharmacology
Volume 142, November 2018, Pages 167-178

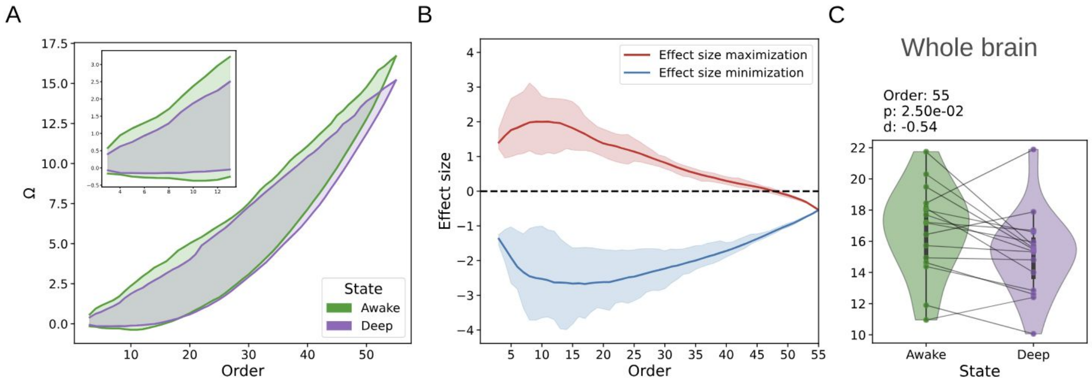
Invited review

The entropic brain - revisited

Robin L. Carhart-Harris



The main effect of Propofol anaesthesia is the reduction of synergy and redundancy

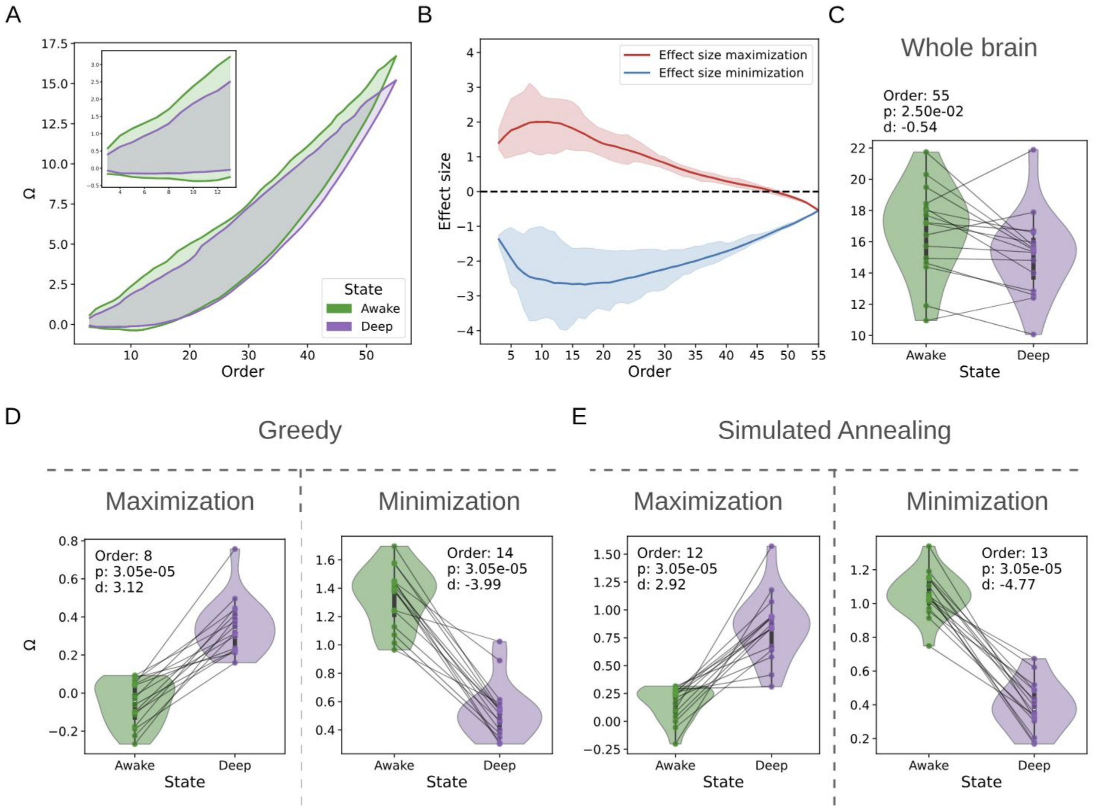


fMRI data.
16 subjects.
55 regions.

Anaesthesia induces slow-waves oscillations, a form of redundant, low-complexity activity.

THOI: An efficient library for computing higher-order interactions enhanced by batch-processing. Belloli and Herzog et al., *arXiv*

The main effect of Propofol anaesthesia is the reduction of synergy and redundancy



- Reconfiguration involved both increases and decreases of the O-information
- Inter-network synergy is lost with anesthesia
- Inter-network redundancy is reduced
- Anesthesia reduces the ability of the brain to integrate functionally segregated networks

THOI: A python library for Higher Order Interactions Analysis Enhanced by batch-processing. Belloli and Herzog et al., *In Preparation*

Applications

Subanesthetic ketamine and portable EEG

Article | Open access | Published: 27 July 2024

High-order brain interactions in ketamine during rest and task: a double-blinded cross-over design using portable EEG on male participants

Rubén Herzog, Florentine Marie Barbey, Md Nurul Islam, Laura Rueda-Delgado, Hugh Nolan, Pavel Prado, Marina Krylova, Igor Izyurov, Nooshin Javaheripour, Lena Vera Danyeli, Zümrüt Duygu Sen, Martin Walter, Patricio O'Donnell, Derek L. Buhl, Brian Murphy & Agustin Ibanez

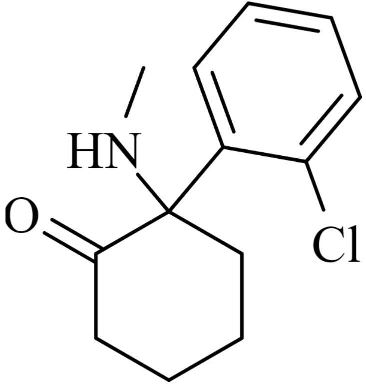
Translational Psychiatry **14**, Article number: 310 (2024) | Cite this article

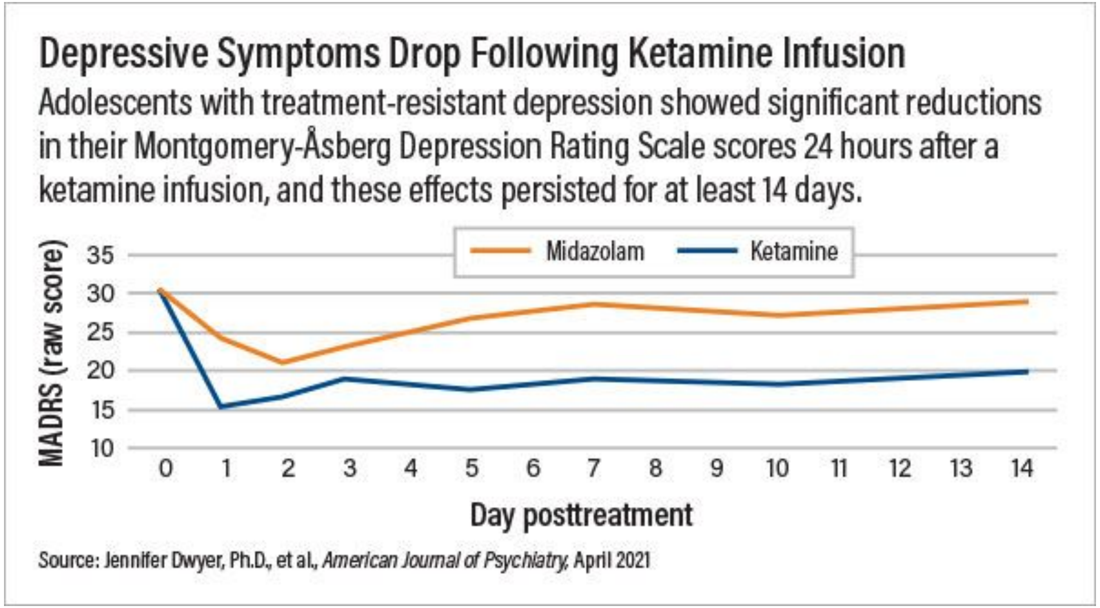
Ketamine

Anaesthetic (high doses), recreative and antidepressant drug (low to mid doses)

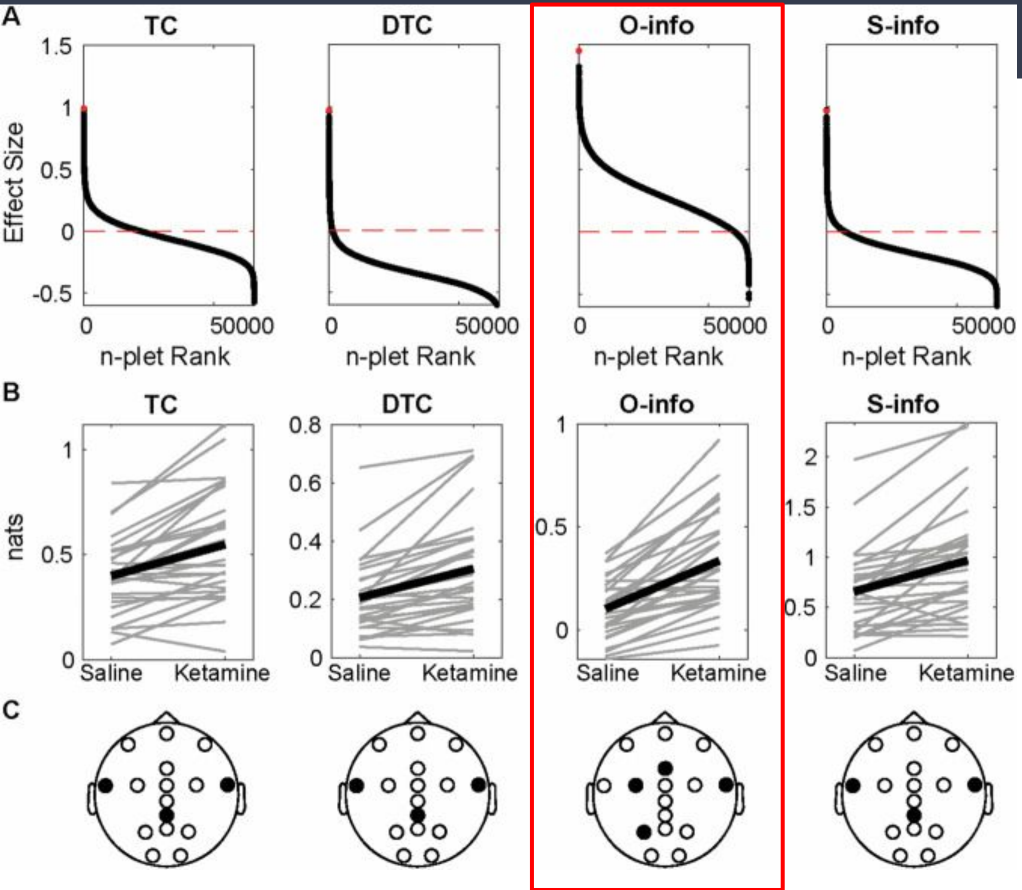
At low-to-mid doses may induce dissociation, derealization, out-of-body experiences and psychedelic experiences.

Effective for treatment-resistant depression



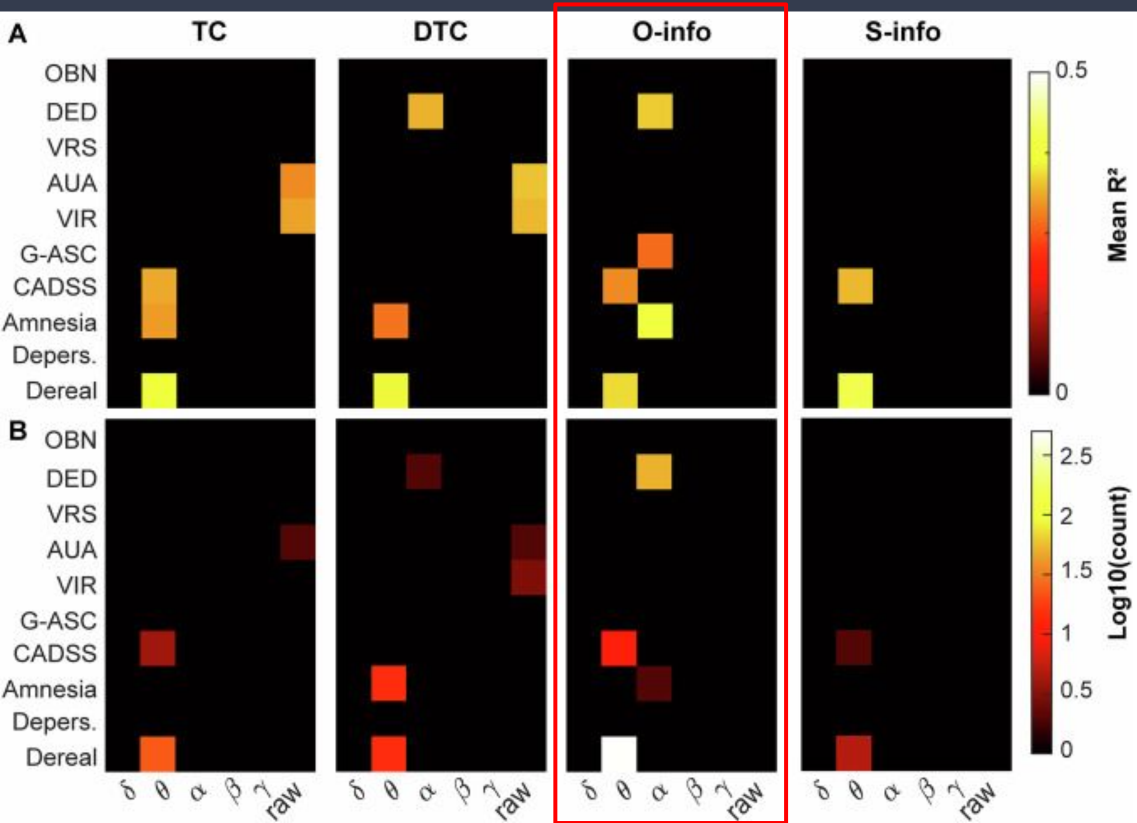


The main effect of subanesthetic Ketamine is the increase in redundancy in the alpha band



Resting state EEG data.
29 subjects.
16 electrodes.

Changes in high-order interactions are associated with changes in subjective experience

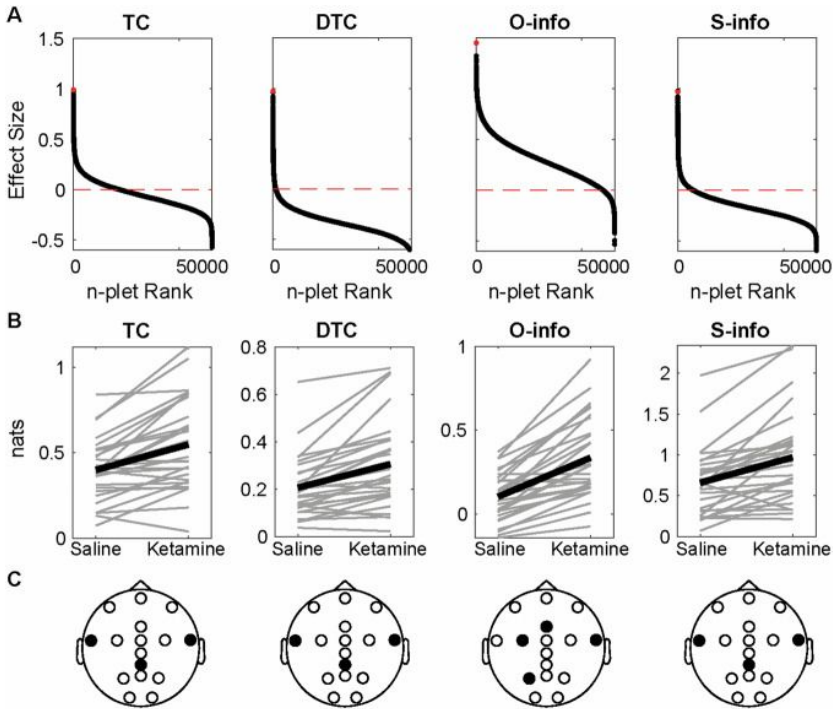


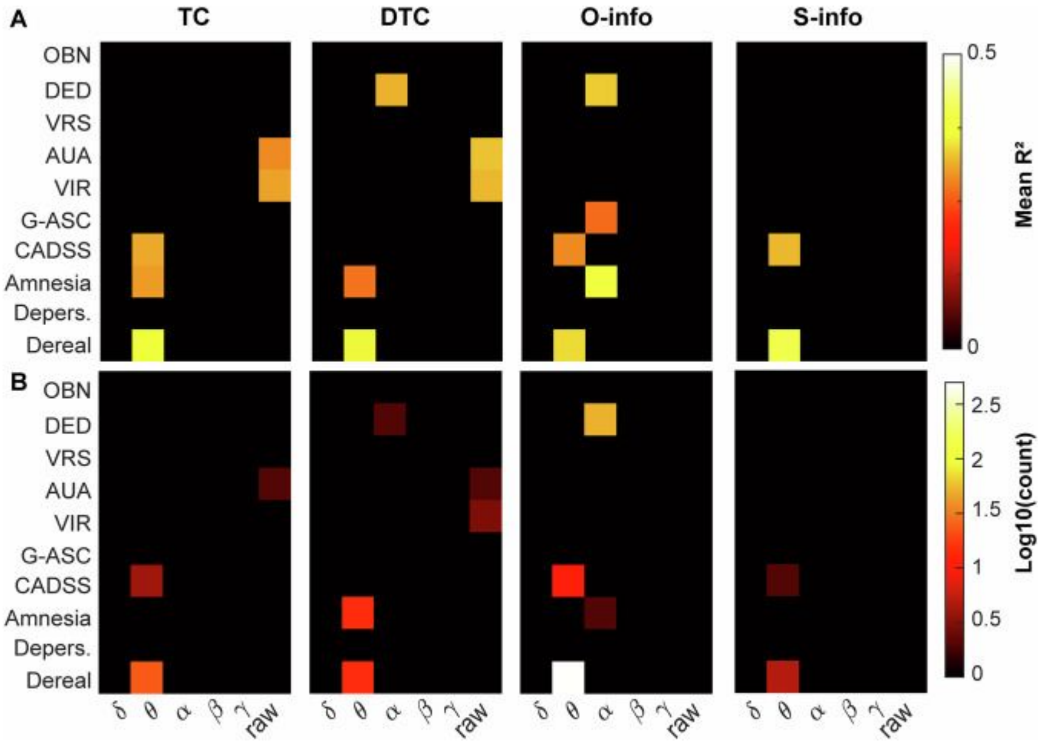
Subjective test

- 5D-Altered states of consciousness test (5D-ASC)
- Clinician-Administered Dissociative States Scale (CADSS)

The largest associations were found for the **O-information** in the theta band with **derealization score.**

O-information can track ketamine-induced changes in the **state** and **dimensions** of consciousness





Applications

Psychedelic experience

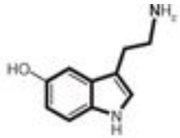
Resting state fMRI recordings under the influence of Psilocybin, LSD, Ketamine and MDMA (not all together)

They induce non-ordinary (altered) states of consciousness.
Profound alterations in cognition, emotion, mood and the experience of space, time, and self.

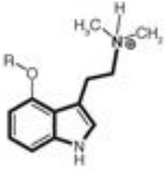
Psilocybin (N=13) & LSD (N=16) (Imperial):
Serotonergic psychedelics. Experiential effects mainly due to their agonism on serotonin 2A receptor.

Ketamine (N=14) (Liege): Glutamatergic dissociative, but complex affinity profile. Anaesthetic at high doses. Antagonist of NMDA glutamate receptors.

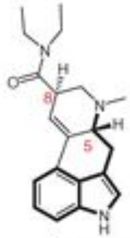
MDMA (N=18) (Imperial): Serotonergic empathogen (increases pro-social behaviour).
Increases serotonin release.



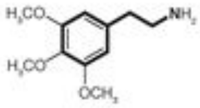
5-Hydroxytryptamine
serotonin



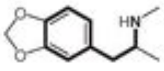
R = H: Psilocin
R = PO_3H: psilocybin



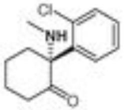
Lysergic acid diethylamide
5R, 8R (+)-LSD



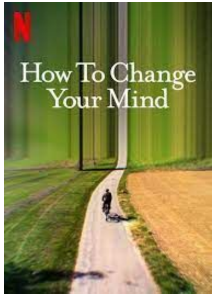
Mescaline



3,4-Methylenedioxy-
methamphetamine
MDMA

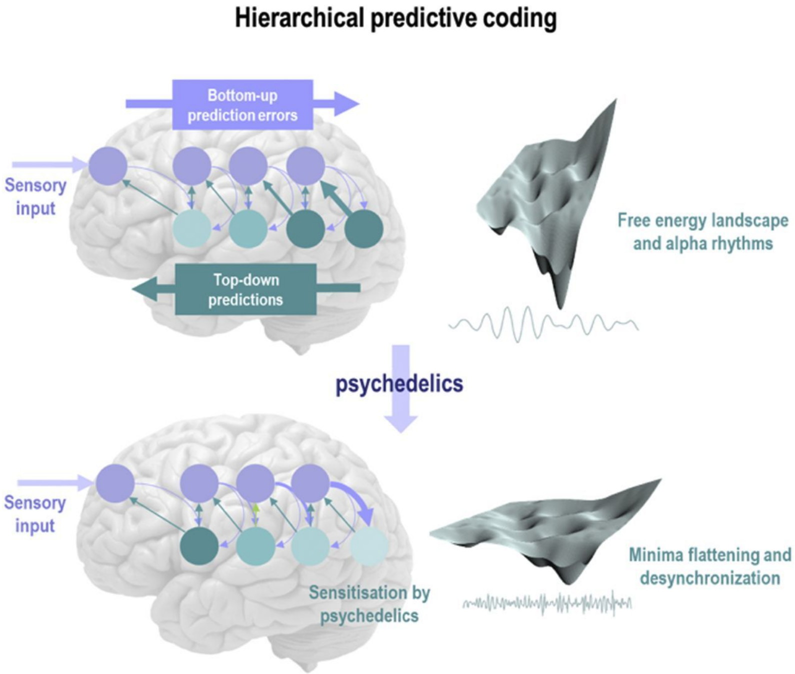


S (+)- Ketamine

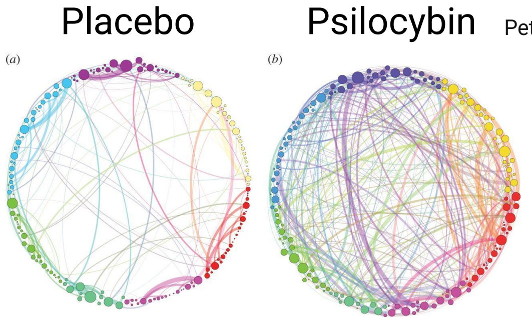


They have an unprecedented potential when used in therapeutic setting for depression, addiction, anxiety, PTSD.

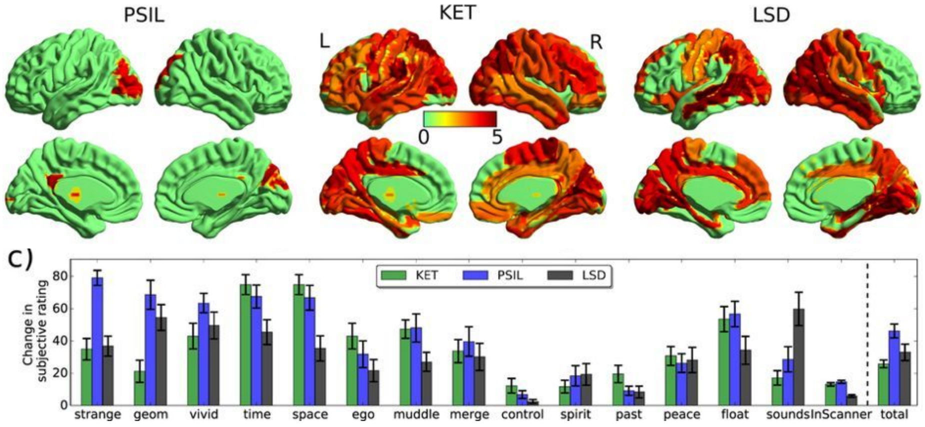
Significant reconfiguration of large-scale functional networks under psychedelics



R. L. Carhart-Harris and K. J. Friston. 2019. **REBUS and the Anarchic Brain**. Pharmacological Reviews

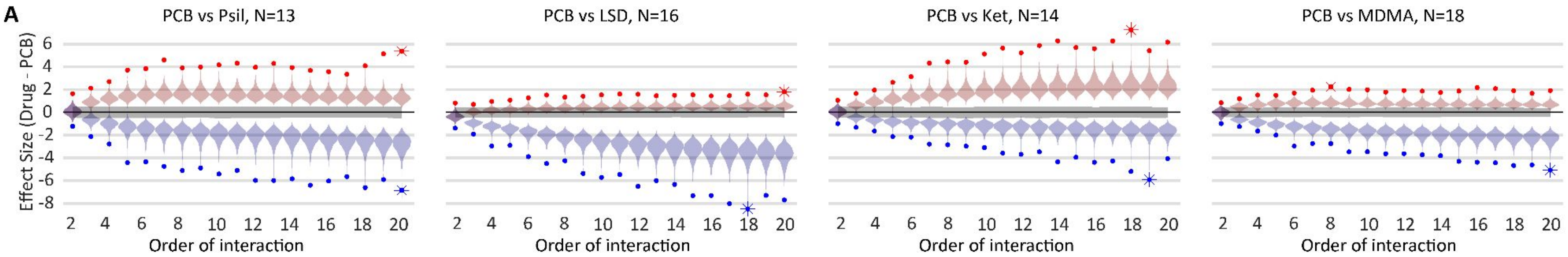


Petri et al. 2014.. **Homological scaffolds of brain functional networks**. Journal of Royal Society Interface.

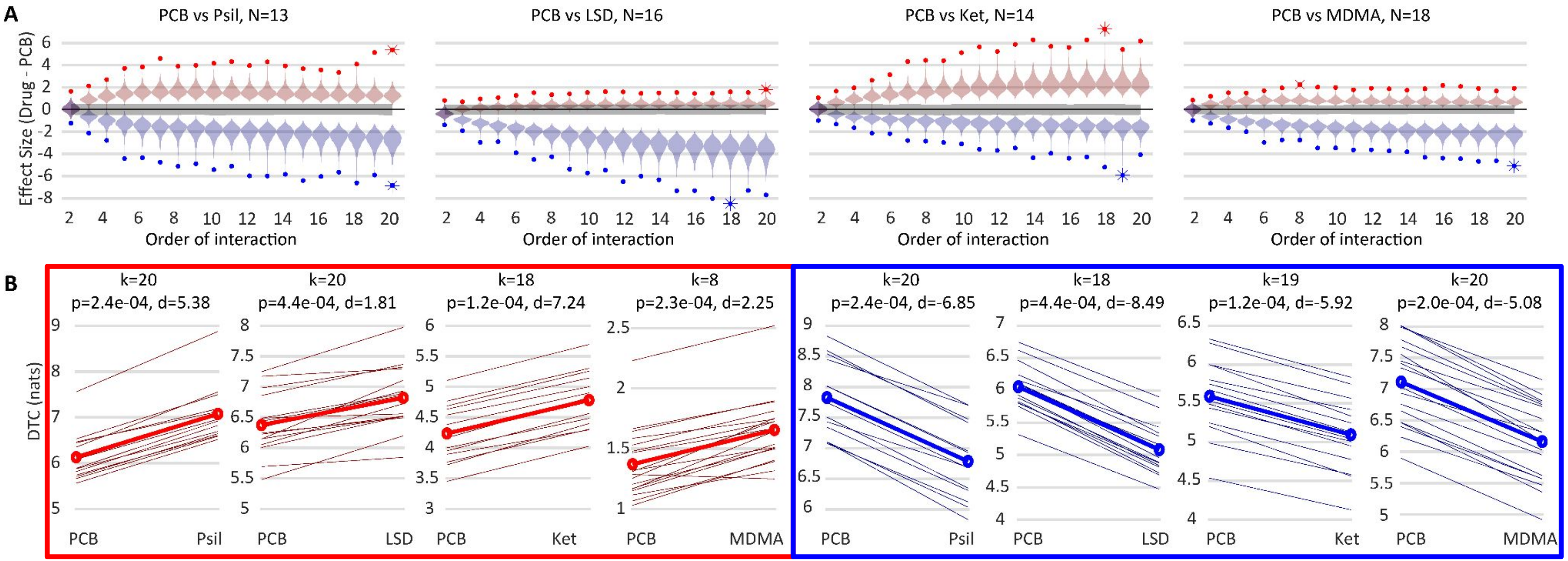


Schartner et al, 2017. **Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin**, Scientific Reports.

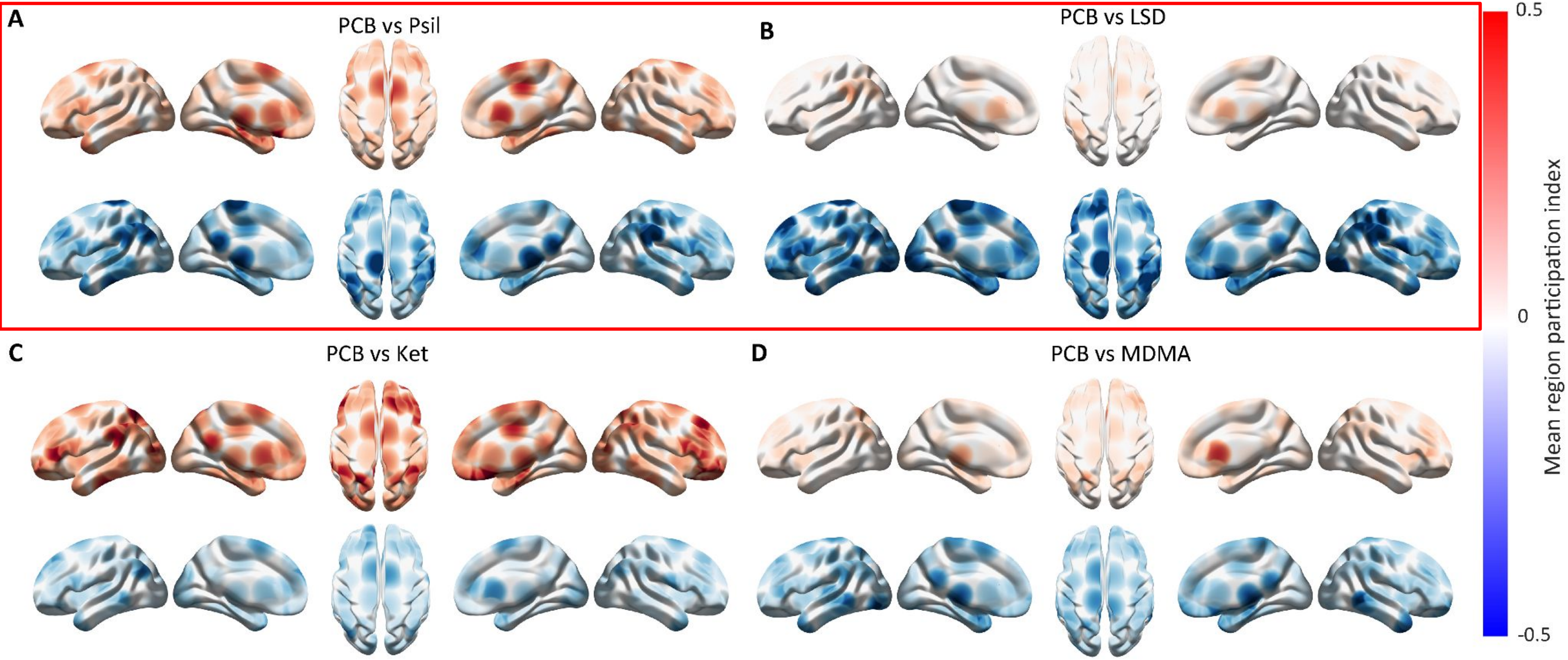
Psychedelics reconfigure brain dynamics at multiple orders of interactions



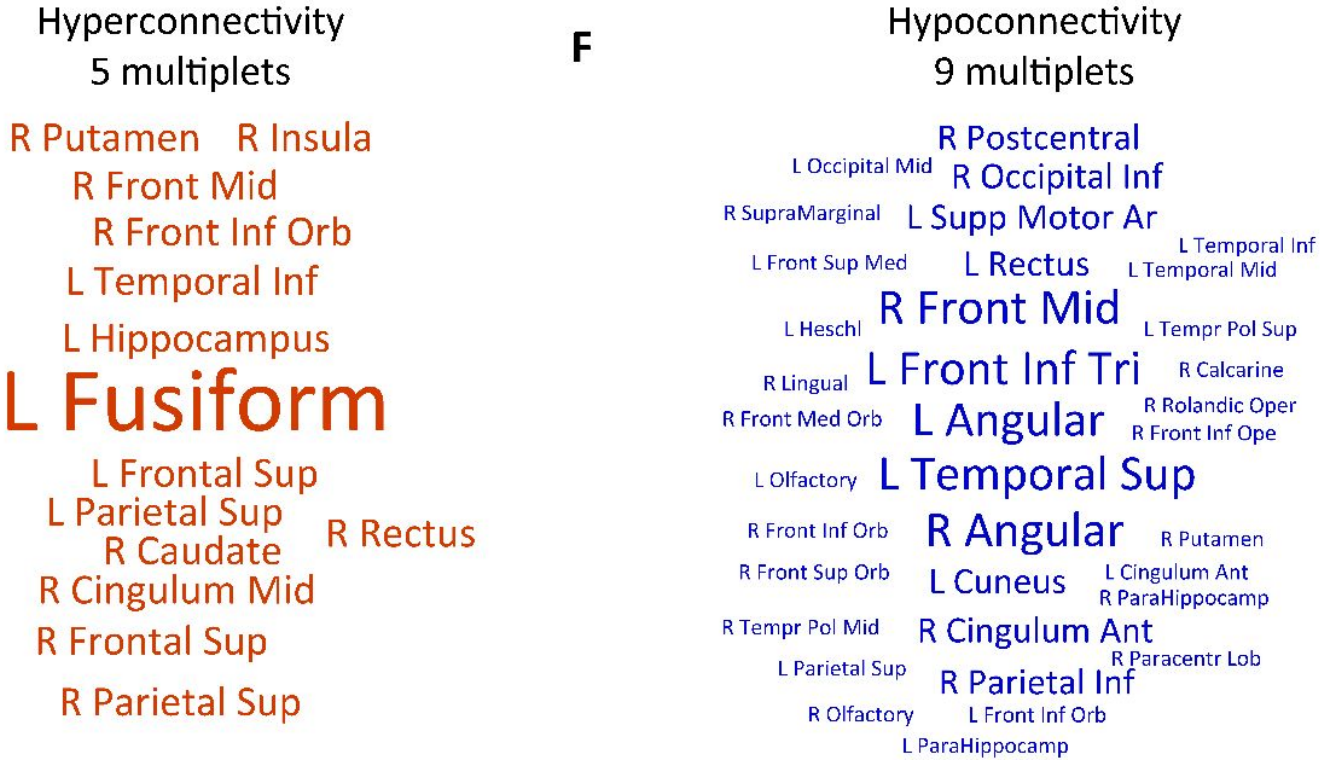
Psychedelics reconfigure brain dynamics at multiple orders of interactions



Each drug induces a specific pattern of high-order hyper and hypo connectivity



Most relevant brain regions

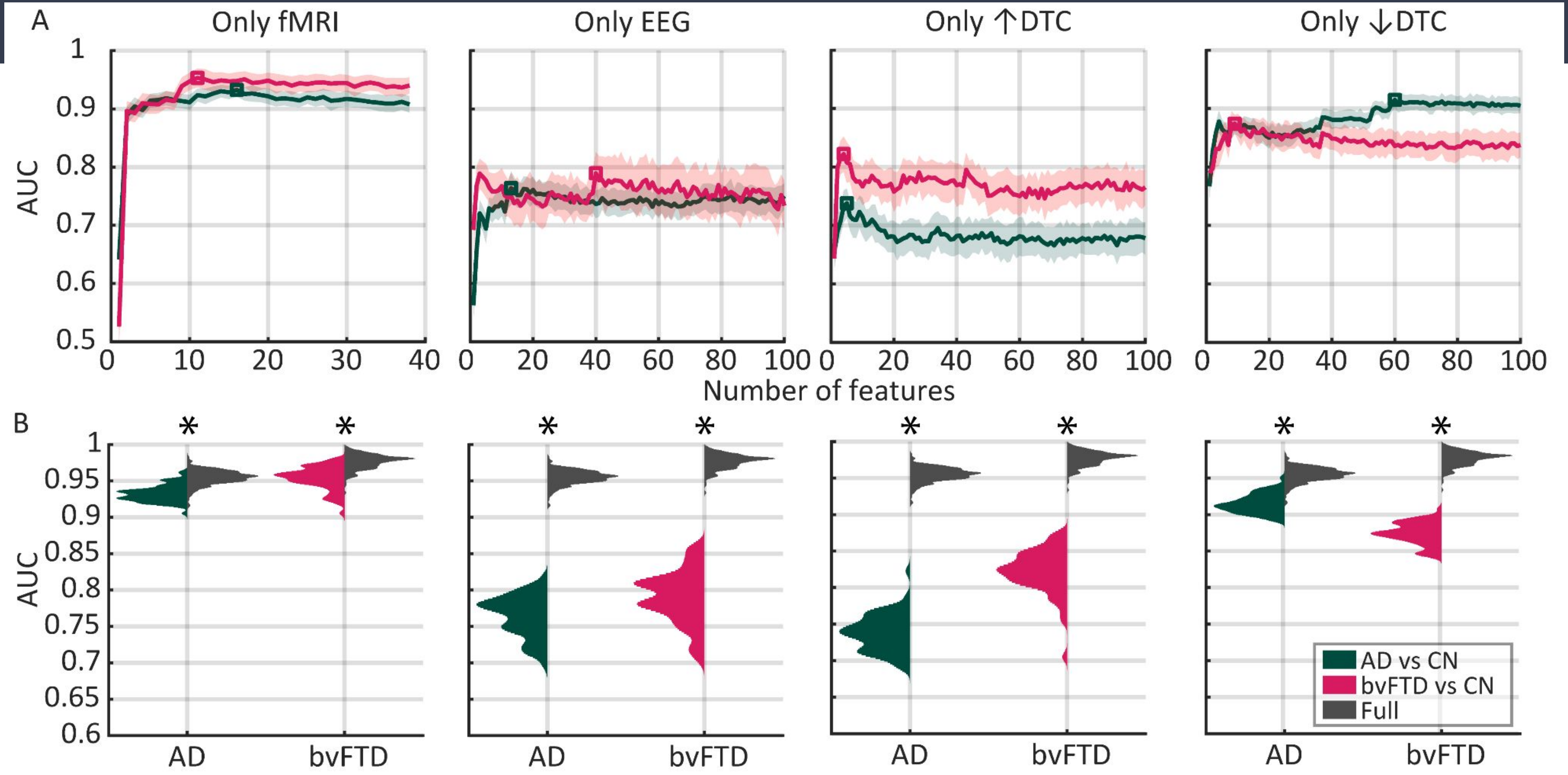


Conclusions

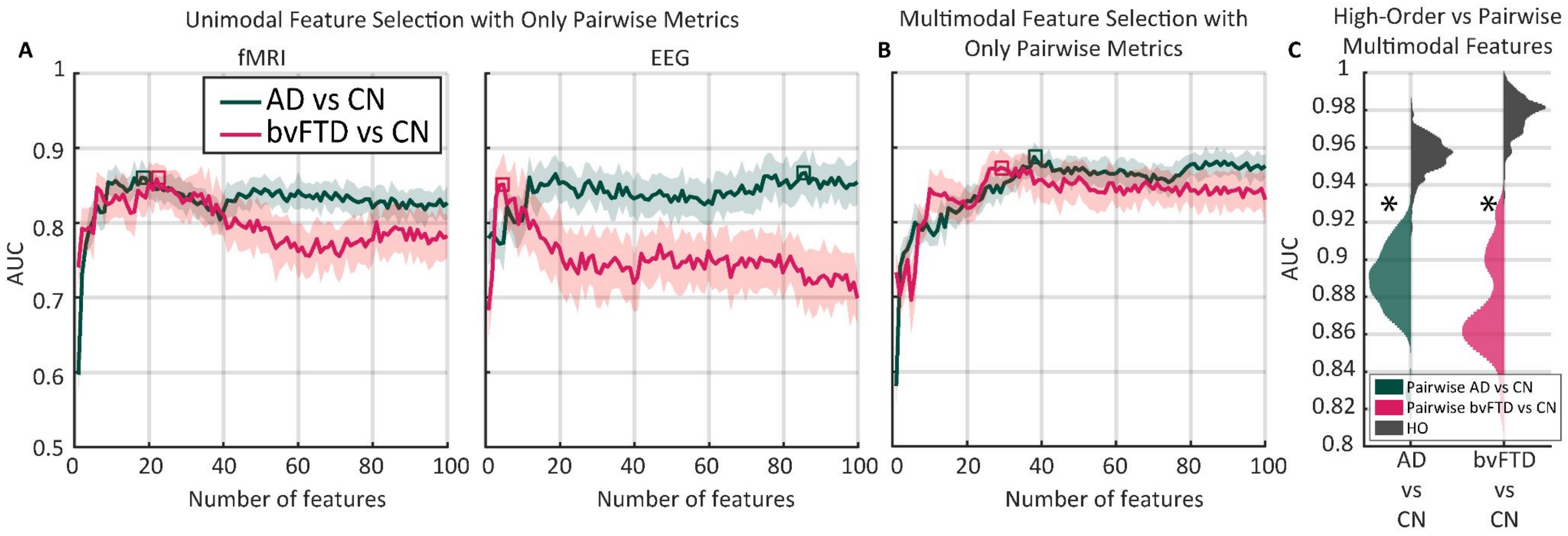
- The brain resting state activity exhibits synergistic interactions
- Brain high order interactions can be disrupted by different conditions
  - Aging increases redundancy
  - Neurodegeneration mainly decreases high-order functional connectivity
  - Anaesthesia reduces synergy and redundancy
  - O-information can track ketamine-induced changes in state and dimensions of consciousness
  - Drug-induced psychedelic states are associated with specific patterns of high-order hyper and hypo connectivity

Tutorial

Specific pathophysiological signatures of neurodegeneration revealed by multimodal data



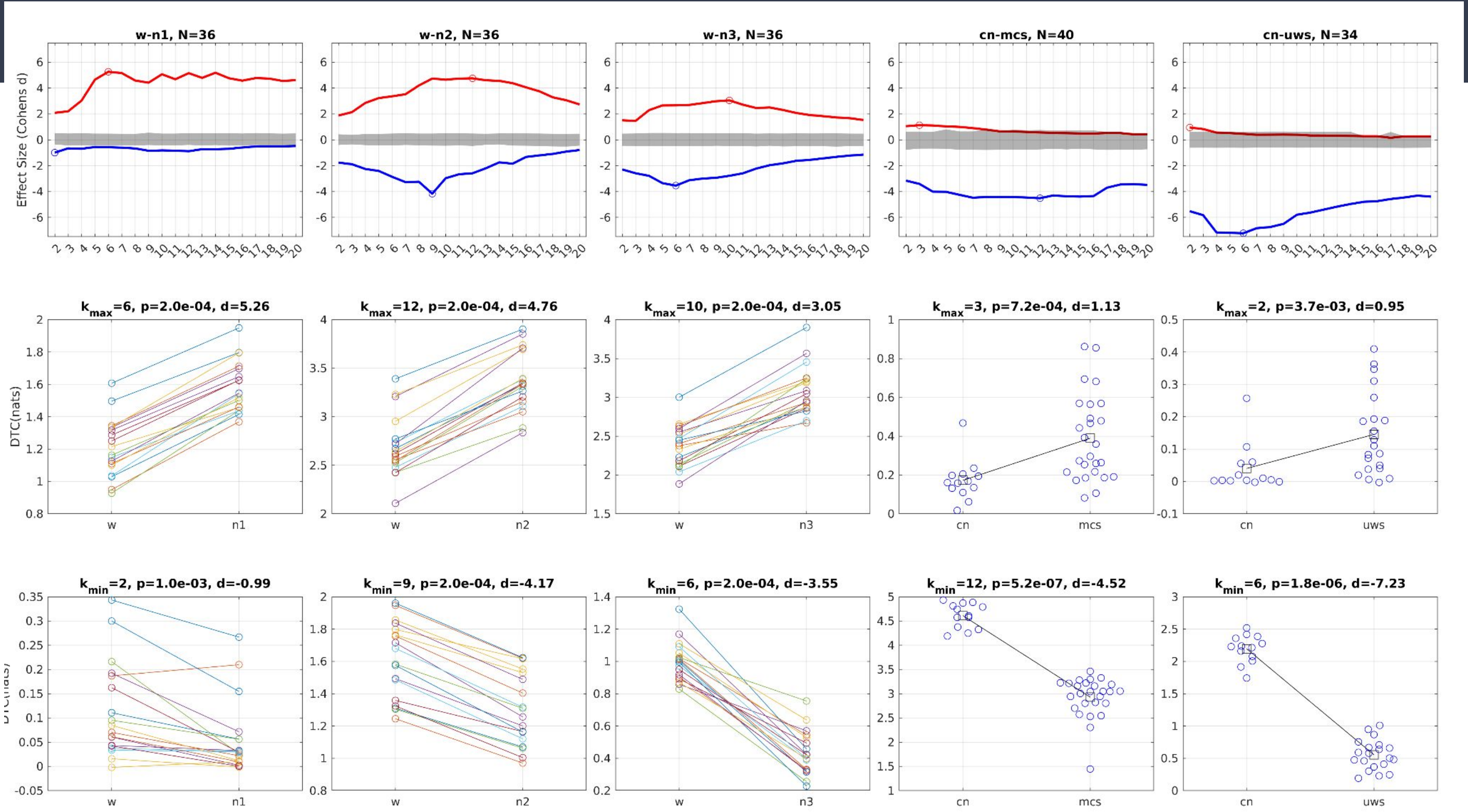
High-order interactions are more parsimonious than pairwise approaches



Linear correlation: Pearson's correlation
Nonlinear correlations: Mutual information.

Using a set of 100 pairs with the largest absolute effect sizes for fMRI and for each EEG frequency band

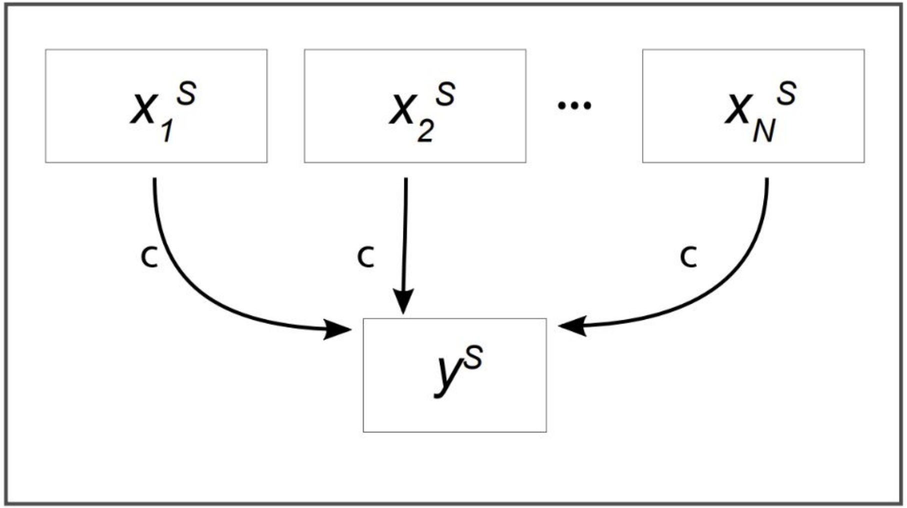
Significant differences between conscious and minimally conscious states (fMRI)



Synergy and Redundancy

Synergy

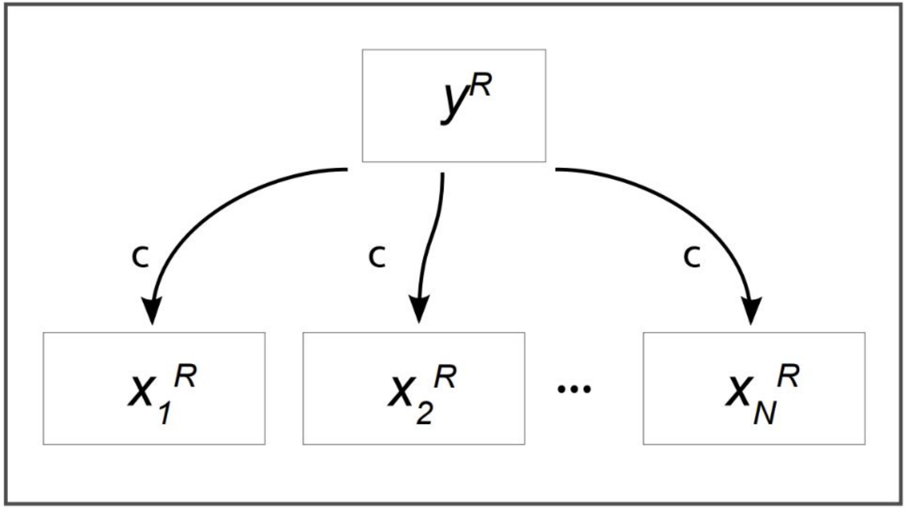
S-system (synergistic)



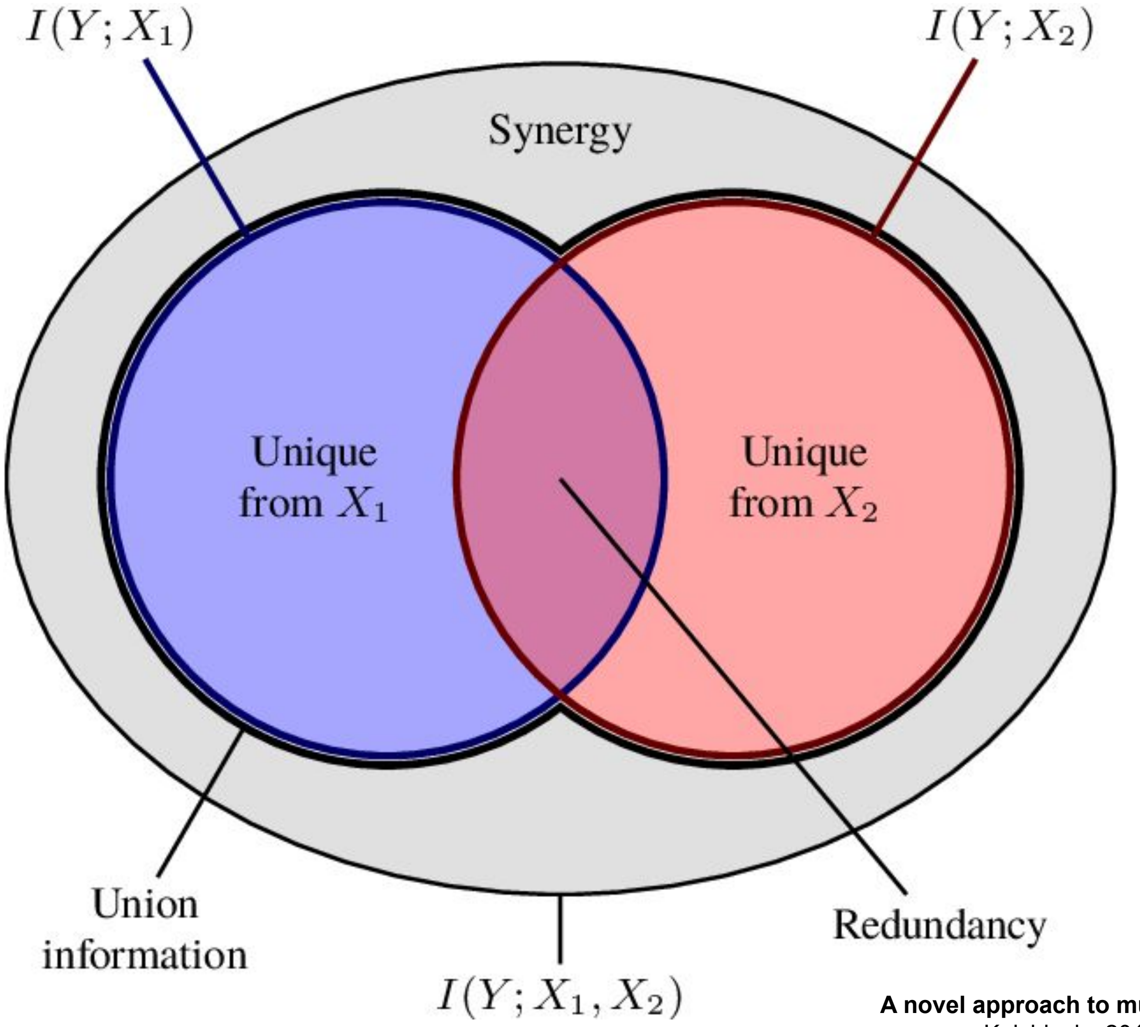
"Collider variables"

Redundancy

R-system (redundant)



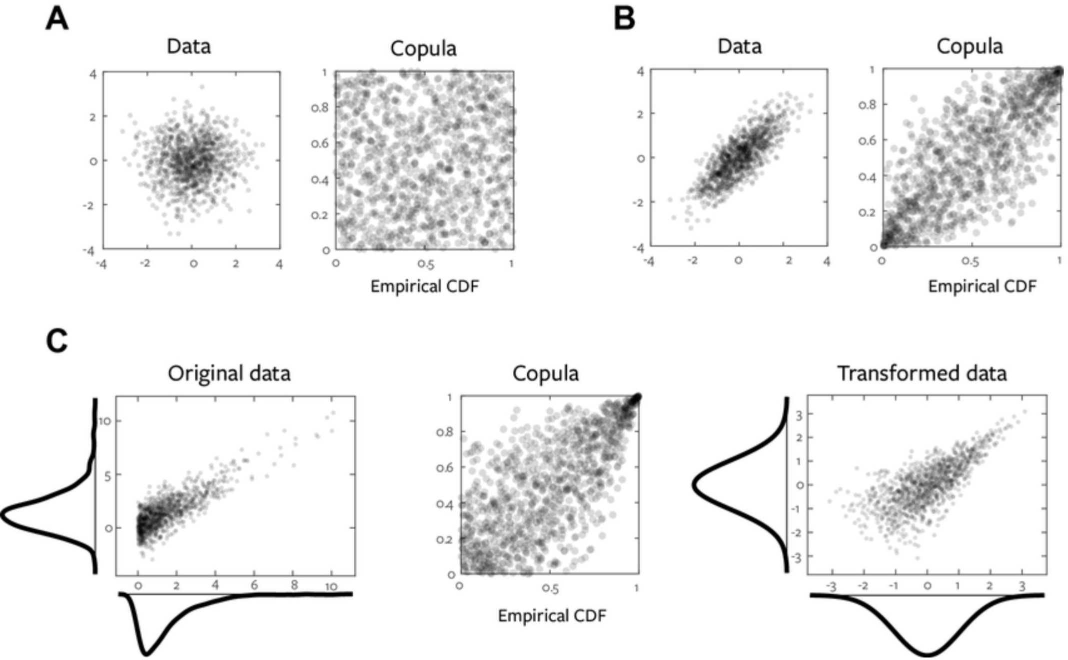
"Confounding variables"



A novel approach to multivariate redundancy and synergy. Kolchisnky 2019.

Estimating Differential Entropy with The Gaussian Copula Approach

A copula captures the dependencies between variables by connecting their cumulative marginal distributions



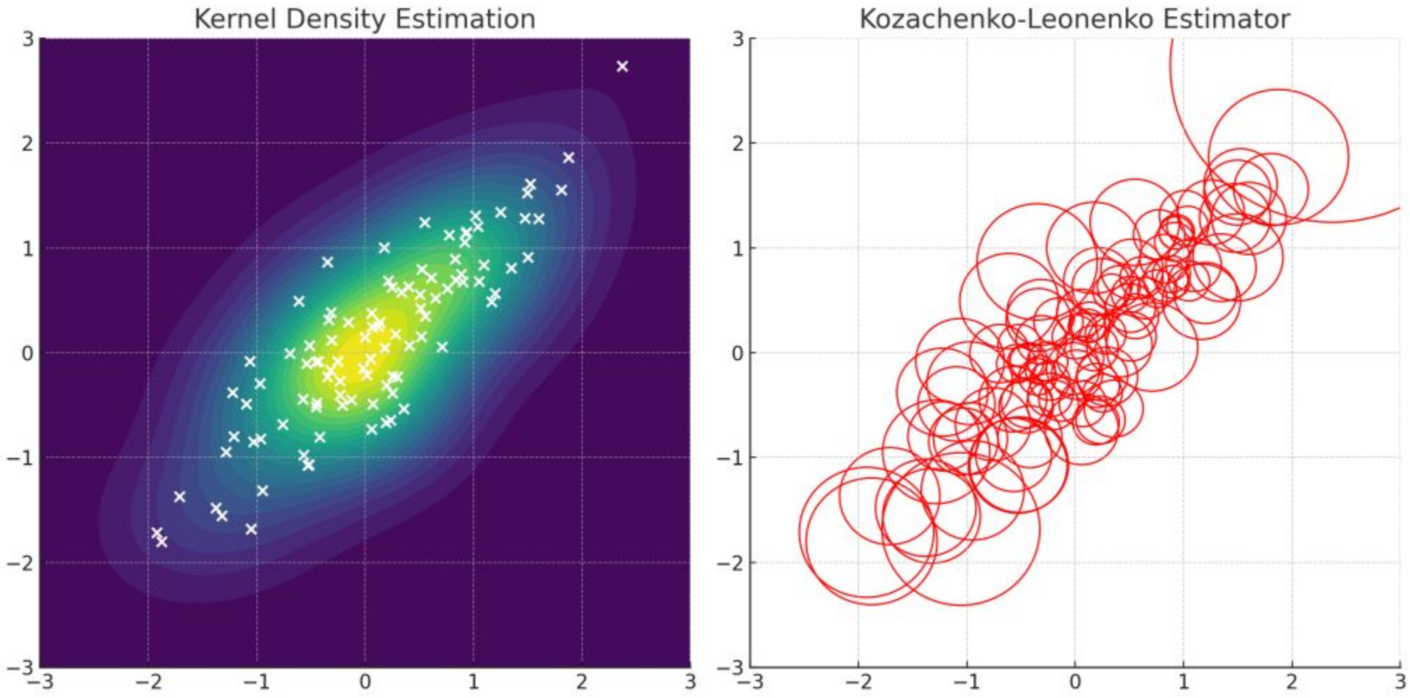
Multivariate Gaussian Entropy

$$H(X^n) = \frac{1}{2}\log((2\pi e)^n|\Sigma|)$$

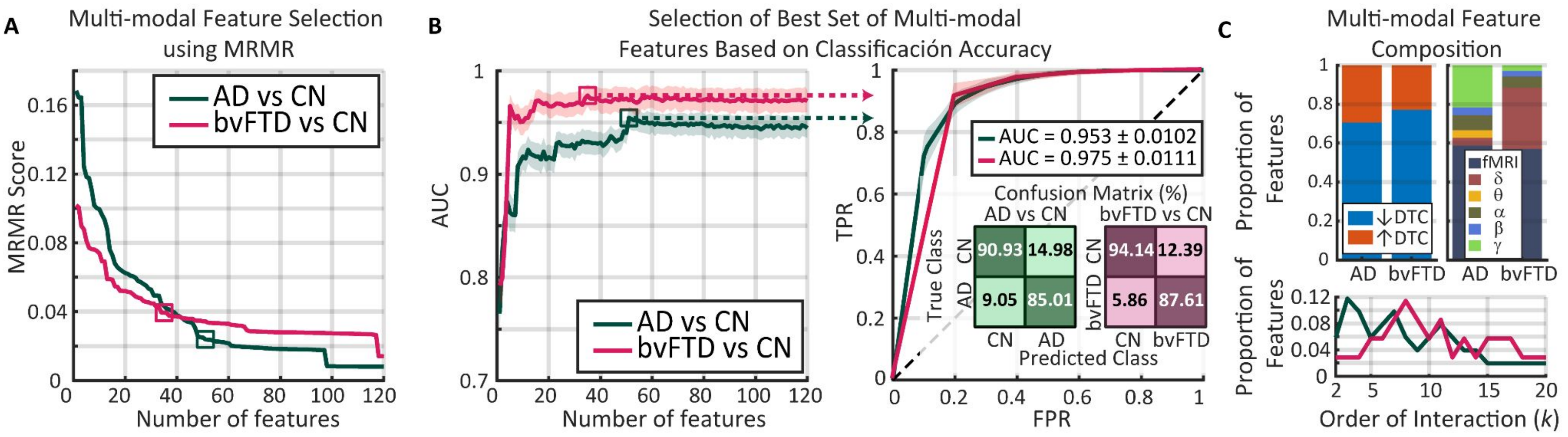
Mutual Information Is Copula Entropy.
Jian and Sun Zengqi, 2011

A statistical framework for neuroimaging data analysis based on mutual information estimated via a Gaussian copula.
Ince et al. 2017.

Non-parametric Estimators

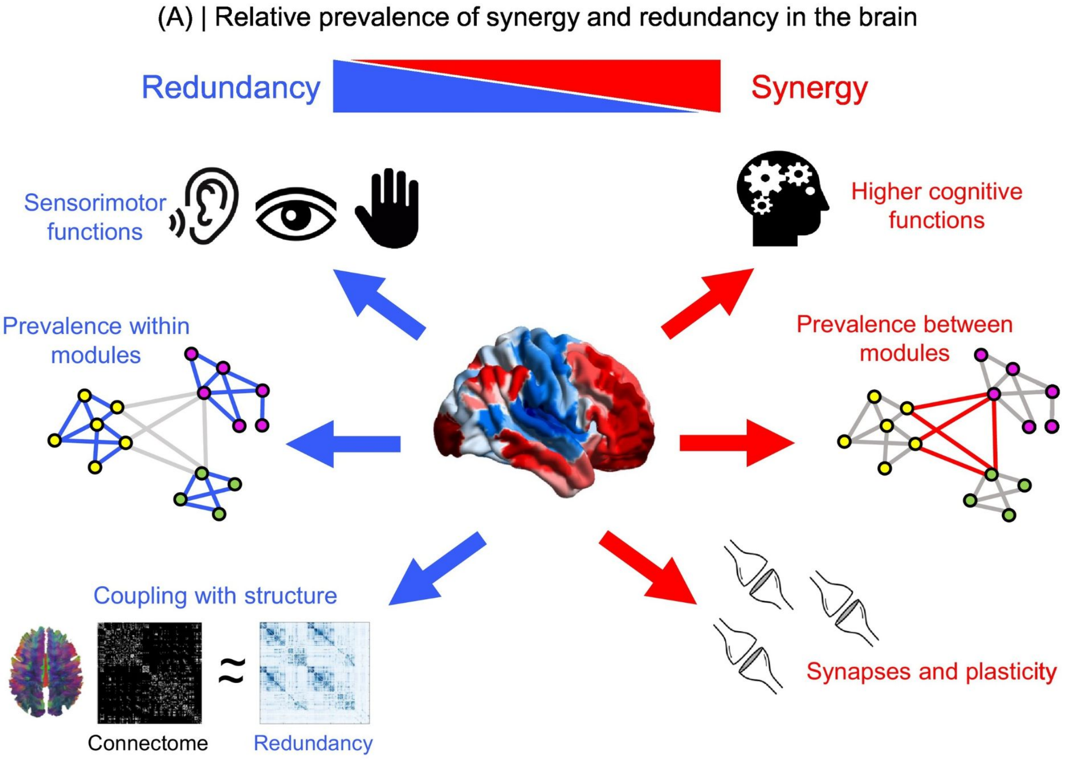


Multimodal integration reveals that Dementia is dominated by high-order hypoconnectivity



- N Features: AD=51, bvFTD=35
- Hypoconnectivity > Hyperconnectivity
- Larger contribution of fMRI than EEG
- Disease-specific contribution of EEG frequency bands
- Larger networks in bvFTD than AD

Synergy, Redundancy and brain functions



Information decomposition and the informational architecture of the brain.
Luppi et al. 2024.