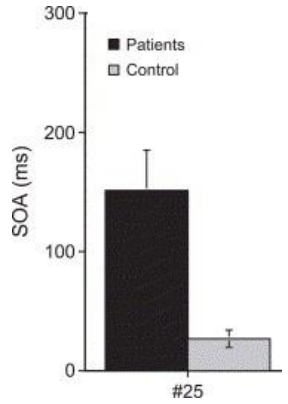
The EEG multiverse of schizophrenia

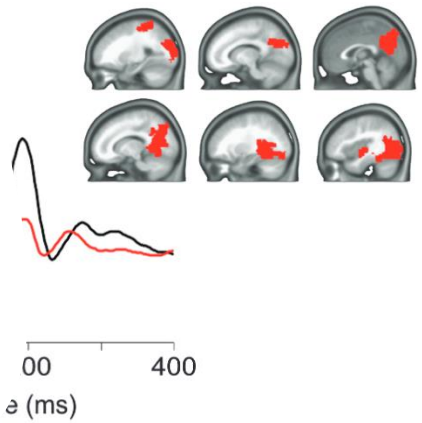
Dario Gordillo

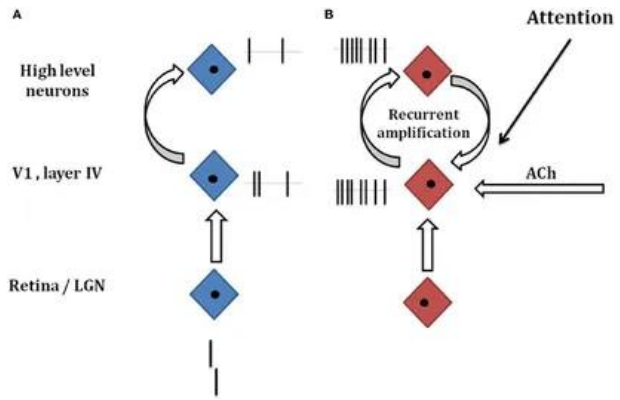
EPFL/CHARITÉ
UNIL-UNIPD Symposium
11.12.2024

The classic approach in schizophrenia research



Left or right?





Association of the nicotinic receptor α7 subunit gene (CHRNA7) with schizophrenia and visual backward masking

George Bakanidze[1], Maya Roinishvili[2,3], Eka Chkonia[3,4], Werner Kitzrow[1], Sarina Richter[1], Konrad Neumann[5], Michael H. Herzog[6], Andreas Brand[7] and Imke Puls[1]*

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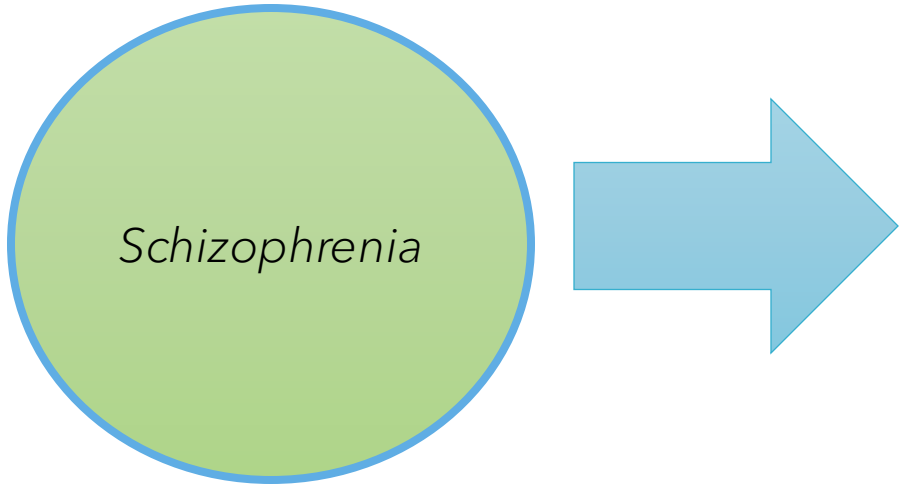
Chkonia et al., 2010, 2012; Plomp et al., 2015; Bakanidze et al., 2009; Herzog et al., 2004, 2013

Patients are impaired in many other domains…



Visual processing

Memory

White matter

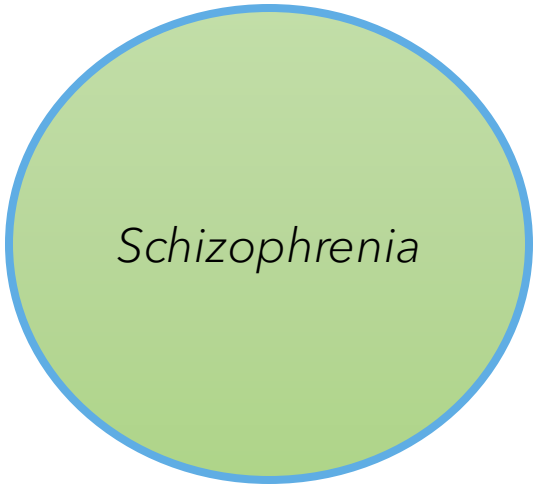
Neurophysiology

Immunology

Skin flushing

…

How do these abnormalities relate with each other?



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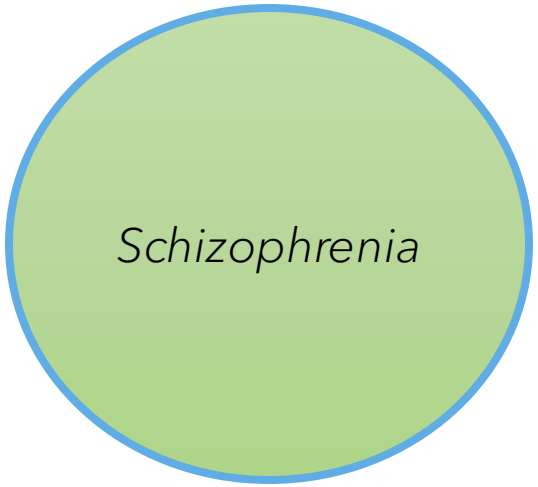
…

All these features point to a common underlying illness…



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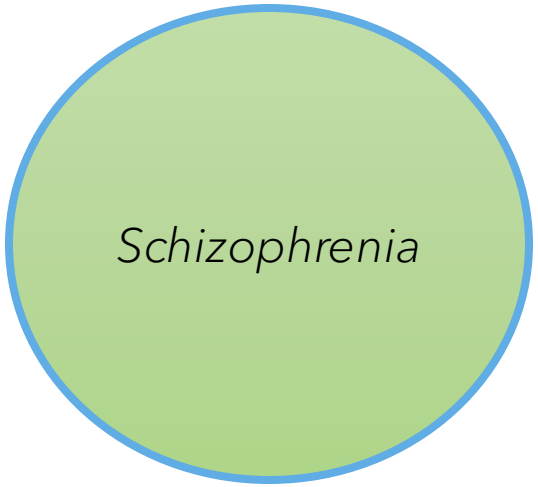
…

They should correlate…



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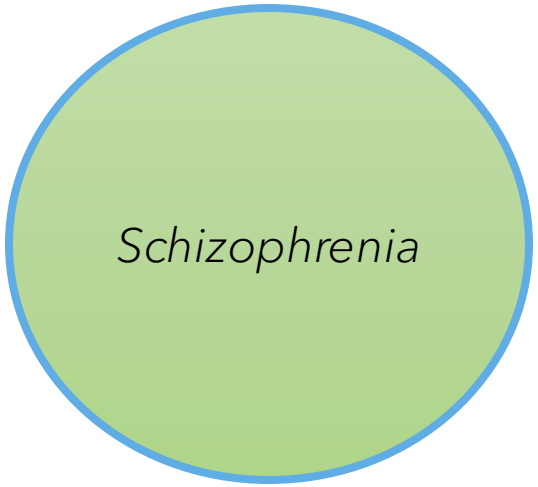
…

However, there are very few studies that have correlated deficits with each other…



Visual processing

Memory

White matter

Neurophysiology

Immunology

Skin flushing

…

Visual processing

Are there correlations between neurophysiological impairments in schizophrenia?

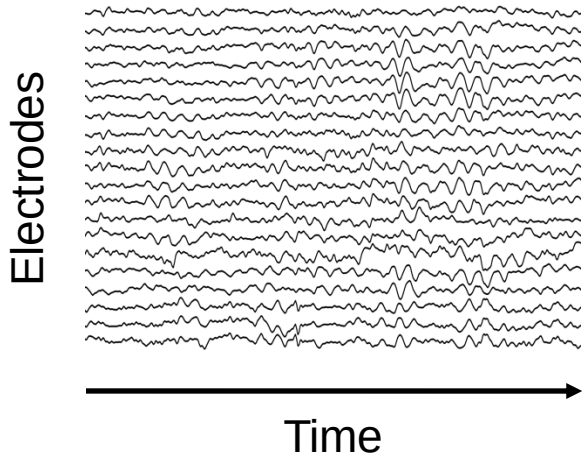
Immunology

Skin flushing

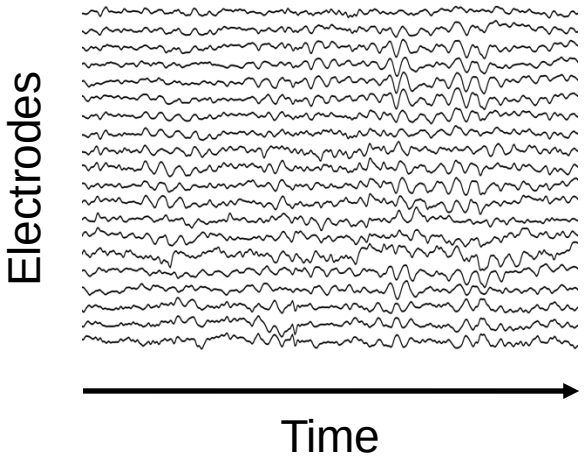
...

Resting-state EEG is a versatile tool to investigate schizophrenia

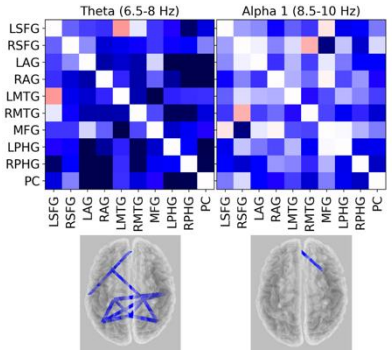
Spontaneous brain activity is recorded for ~5min



Same data, several mechanisms for schizophrenia



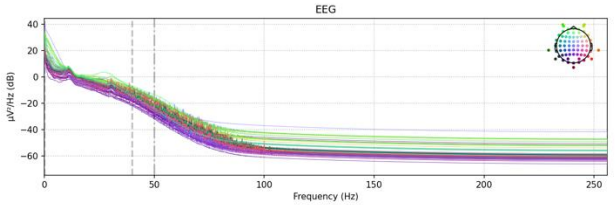
Connectivity



Di Lorenzo et al., 2015; Andreou et al., 2018

- Increased connectivity: Impairments in neural inhibition
- Decreased connectivity: Impairments in attentional processing

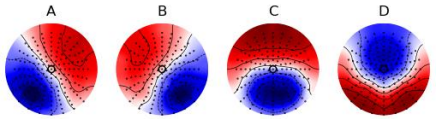
Spectral analysis



Venables et al., 2008

- Increased delta, theta, and alpha band activity: Impairments in dopaminergic function
- Increased activity in the beta band: Cortical hyperexcitability

EEG microstates



Rieger et al, 2016

- Impairments in attentional control
- Genetic risk

...

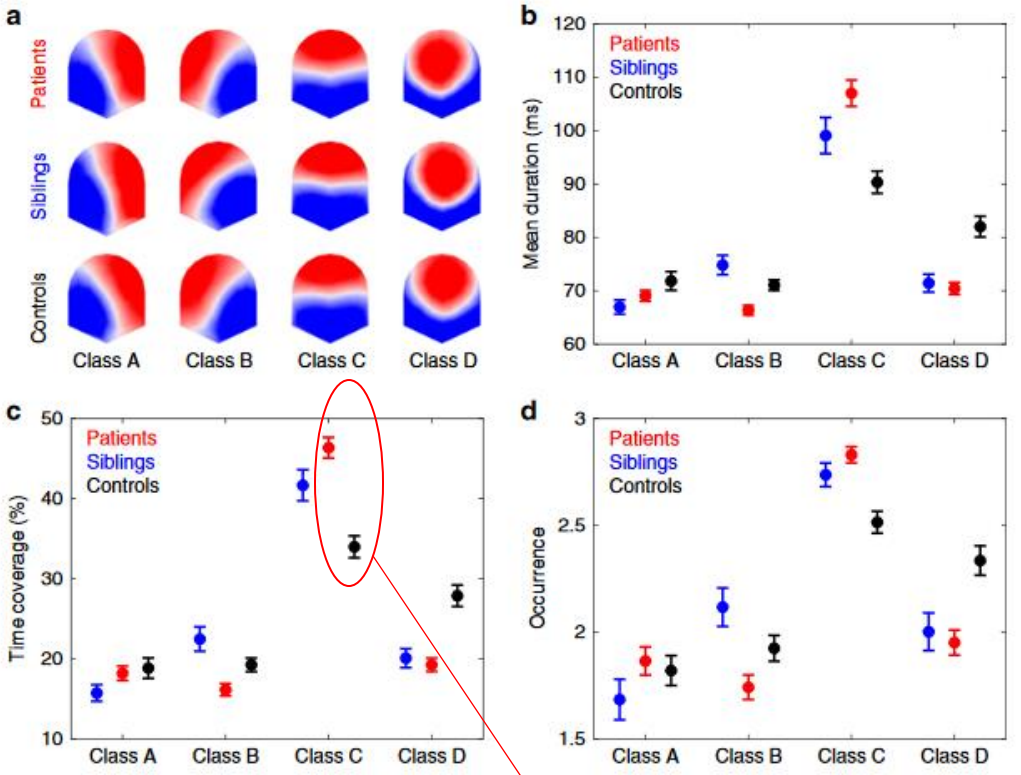


Table 1 Patients vs. controls for all microstate parameters and for each microstate class.

Parameter	Microstate	*p*	p_{holm}	*d*	95% CI
Mean duration	Class A	0.054	0.270	−0.293	[−0.593, 0.008]
	Class B	**0.003**	**0.018**	**−0.454**	**[−0.756, −0.151]**
	Class C	**1.315e − 4**	**0.001**	**0.590**	**[0.284, 0.894]**
	Class D	**3.010e − 6**	**3.311e − 5**	**−0.732**	**[−1.039, −0.423]**
Time coverage	Class A	0.449	0.898	−0.110	[−0.409, 0.189]
	Class B	0.074	0.296	−0.271	[−0.571, 0.029]
	Class C	**1.452e − 7**	**1.742e − 6**	**0.827**	**[0.515, 1.137]**
	Class D	**3.445e − 6**	**3.445e − 5**	**−0.725**	**[−1.032, −0.416]**
Occurrence	Class A	0.882	0.898	0.023	[−0.276, 0.322]
	Class B	0.112	0.336	−0.247	[−0.547, 0.053]
	Class C	**1.170e − 4**	**0.001**	**0.602**	**[0.296, 0.907]**
	Class D	**1.620e − 4**	**0.001**	**−0.578**	**[−0.882, −0.272]**

Post hoc pairwise group comparisons of EEG microstate dynamics of patients ($n = 101$) and controls ($n = 75$). *p* values refer to main effects of group following Group × Gender ANCOVAs with Education as a covariate; degrees of freedom (df) of the numerators are 1 and df for the denominators are 171. p_{holm} values refer to Bonferroni-Holm corrected *p* values for 12 comparisons (3 parameters × 4 classes). η^2's were converted to Cohen's *d*'s. Statistically significant differences are indicated in bold.

da Cruz et al., 2023

Methods

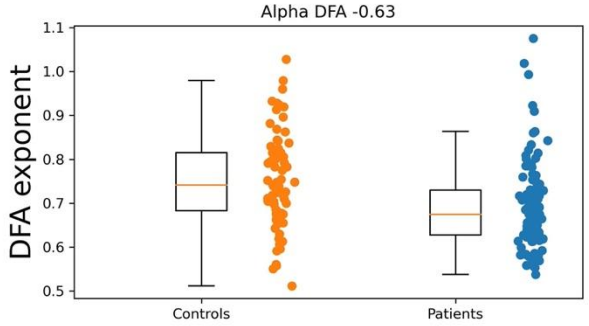
- Participants:
  - 121 patients with schizophrenia and 75 healthy controls
- EEG analysis:
  - We applied several analysis methods to the very same resting-state EEG data and obtained 194 EEG features (e.g., alpha band power)
- Statistical analysis:
  - Group comparisons
  - Correlation analysis

Results

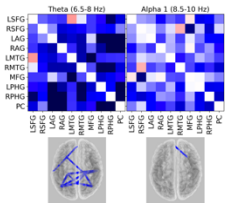
69 out of 194 EEG features showed significant group differences

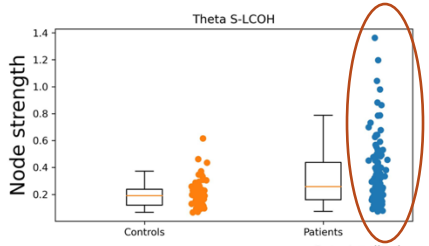
Cohen's *d* ranged from 0.5 to 1
Discriminability : 60 to 70%

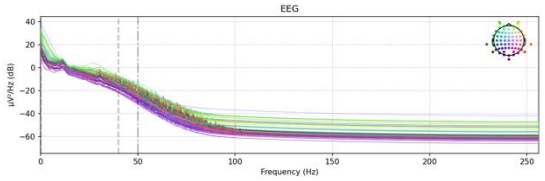
A diverse set of features showed differences between patients and controls

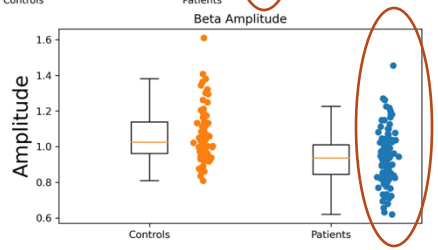


Neurophysiological alterations in schizophrenia

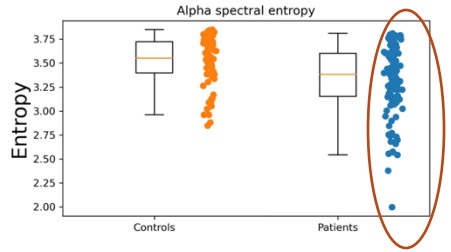


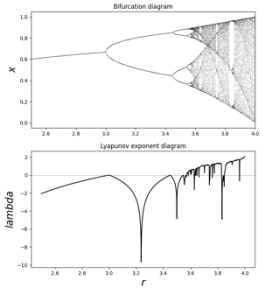


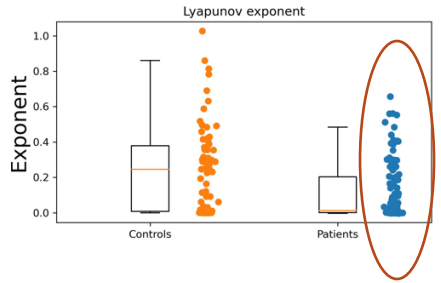


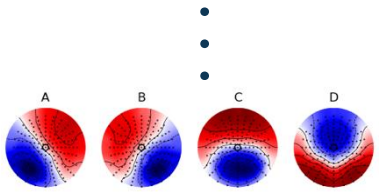


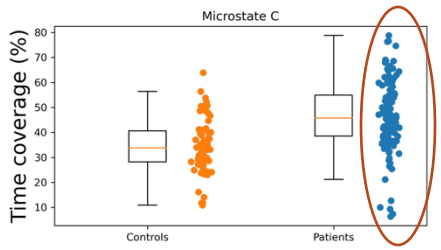
$$H = -\sum_{i=1}^{N} p_i \log(p_i)$$



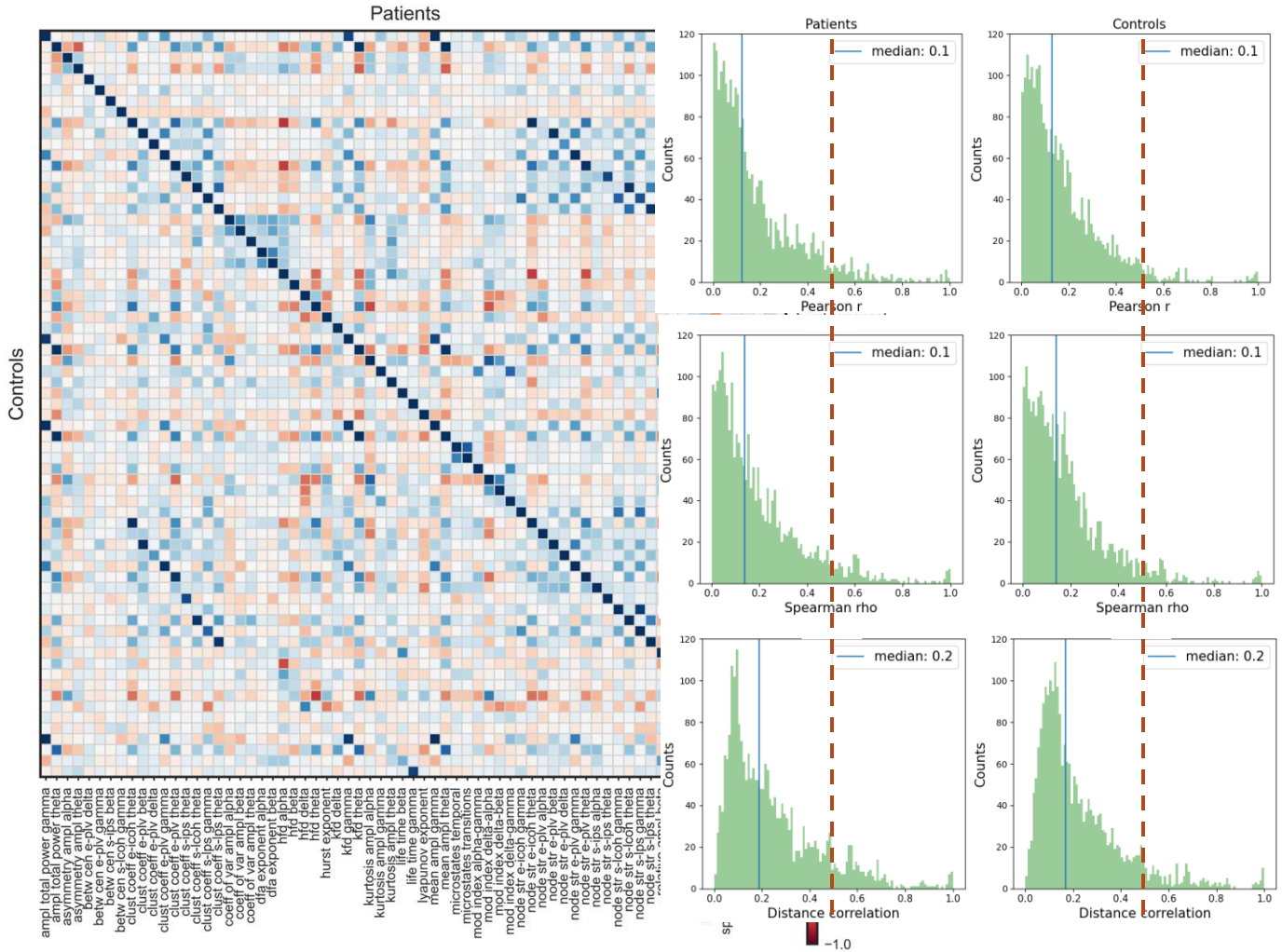


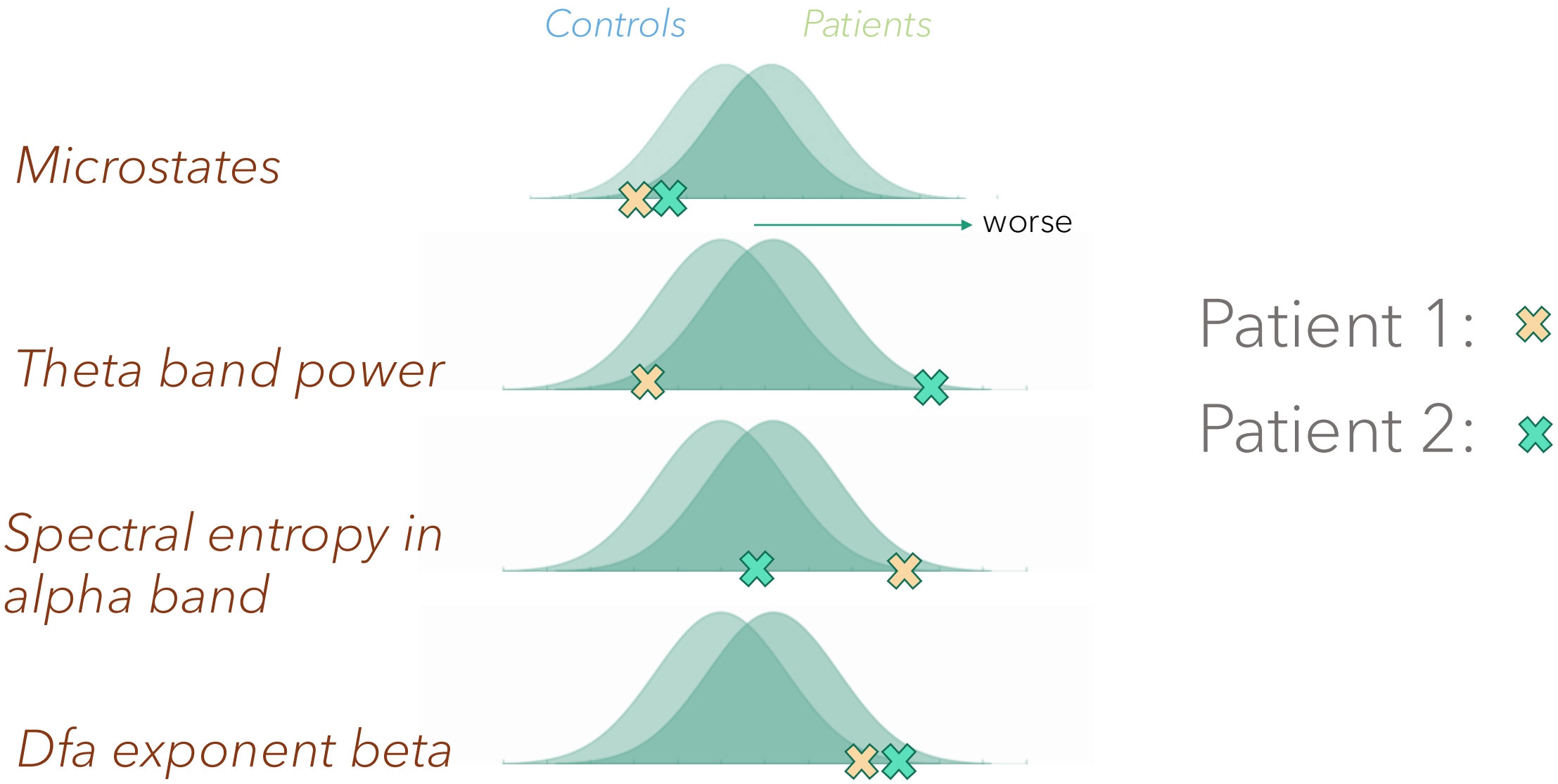




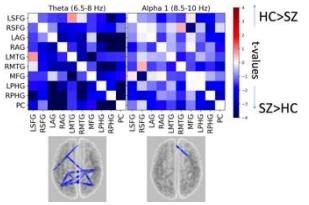


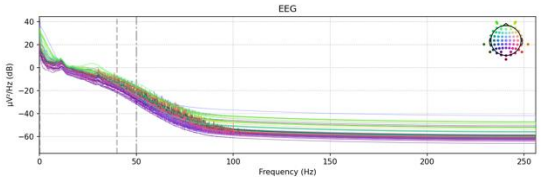
Same data, a range of candidate mechanisms, but low correlations




Controls
Patients
Microstates
worse
Theta band power
Spectral entropy in alpha band
Dfa exponent beta
Patient 1:
Patient 2:

Neurophysiological alterations in schizophrenia





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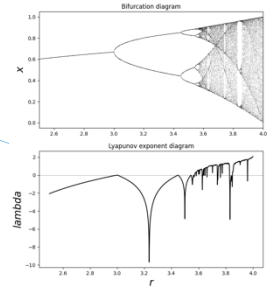
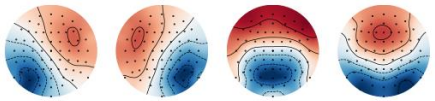
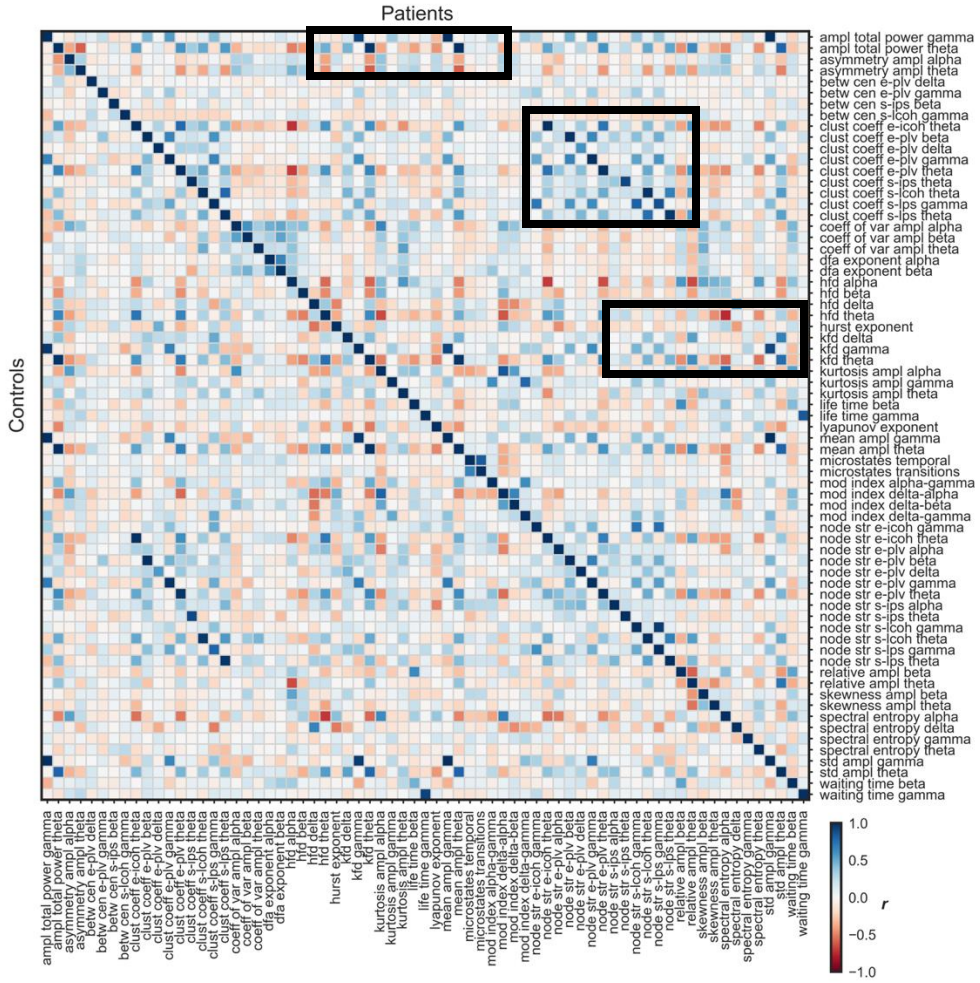




Why significant group differences and low correlations?

- Test-retest reliability
- Large effects are not so large
- Idiosyncratic measures
- Heterogeneity

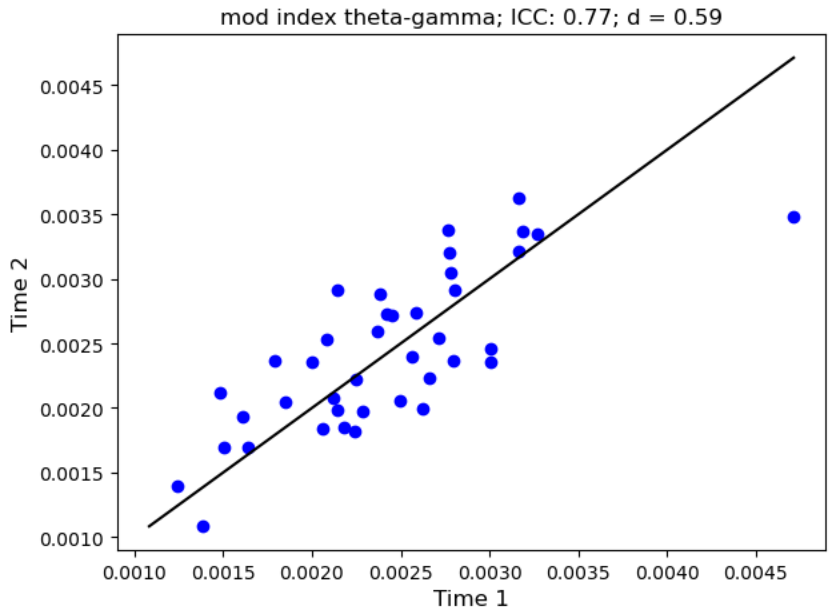
Low test-retest reliability?



- If noise rules, there should not be correlations at all
- Previous studies show that some EEG features have adequate reliability:
  - Microstates (Khanna et al., 2014)
  - DFA exponents (Nikulin et al., 2004)
  - Spectral amplitudes and entropy measures (Gudmundsson et al., 2007)
  - …

Many features are also remarkably stable even after several years

Patients (N=40)	ICCs
19/82 (23%)	<0.4 (poor)
15/82 (18%)	0.4 < ICC < 0.59 (fair)
36/82 (44%)	0.6 < ICC < 0.75 (good)
12/82 (15%)	ICC >0.75 (excellent)



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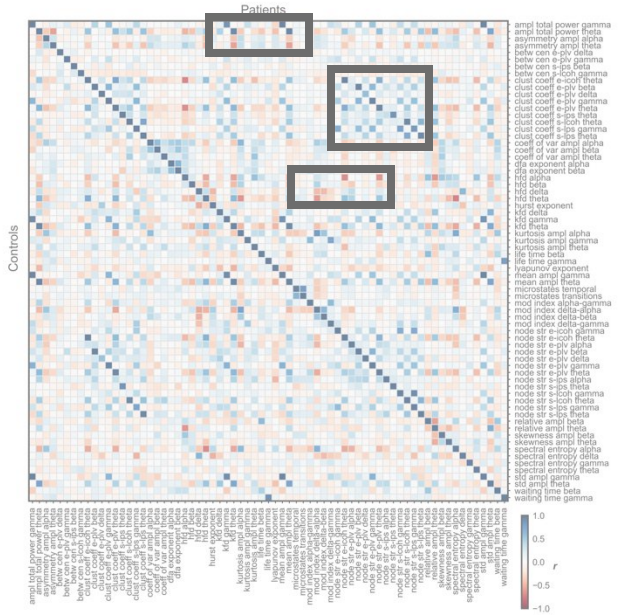
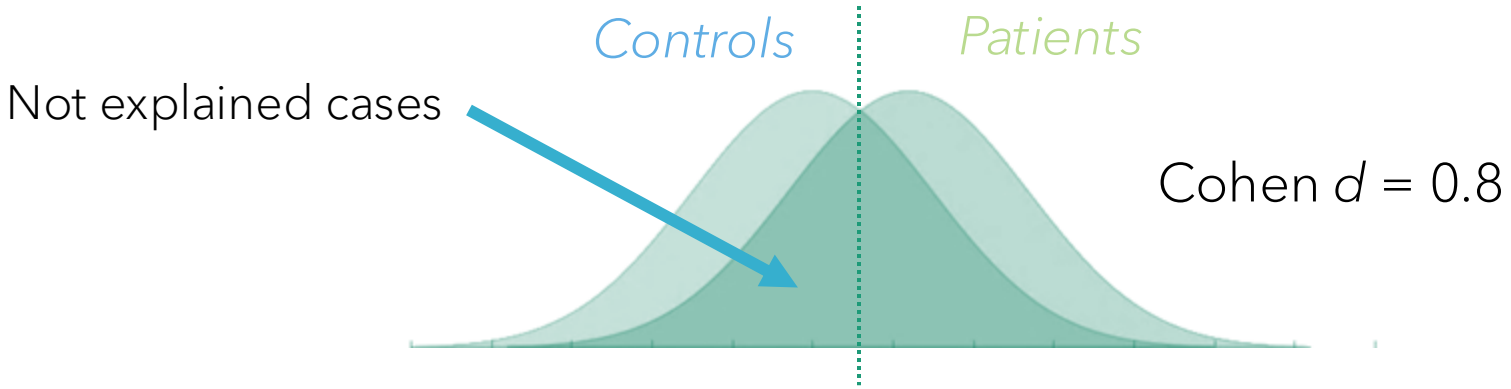


Large effect sizes are not so large? : Cohen *d* and discriminability



- For a Cohen *d* of 0.8, the discriminability is 65%: 35% of the patients do not show the effect
- A discriminability of 80% corresponds to a Cohen *d* of 1.68

Large effect sizes are not so large? : Discriminability in other fields

- Visual masking ~72 %
- Memory ~70%
- Cortical thickness ~60%
- White matter ~58%
- Sensorimotor function ~60%
- Neurophysiology
  - ~66% - P300
  - ~78% - P50
  - ~63% - N170

Aleman et al., 1999; Bramon et al., 2004; McCleery et al., 2015; Kelly et al., 2018; van Erp et al., 2018; San-Martin et al., 2020

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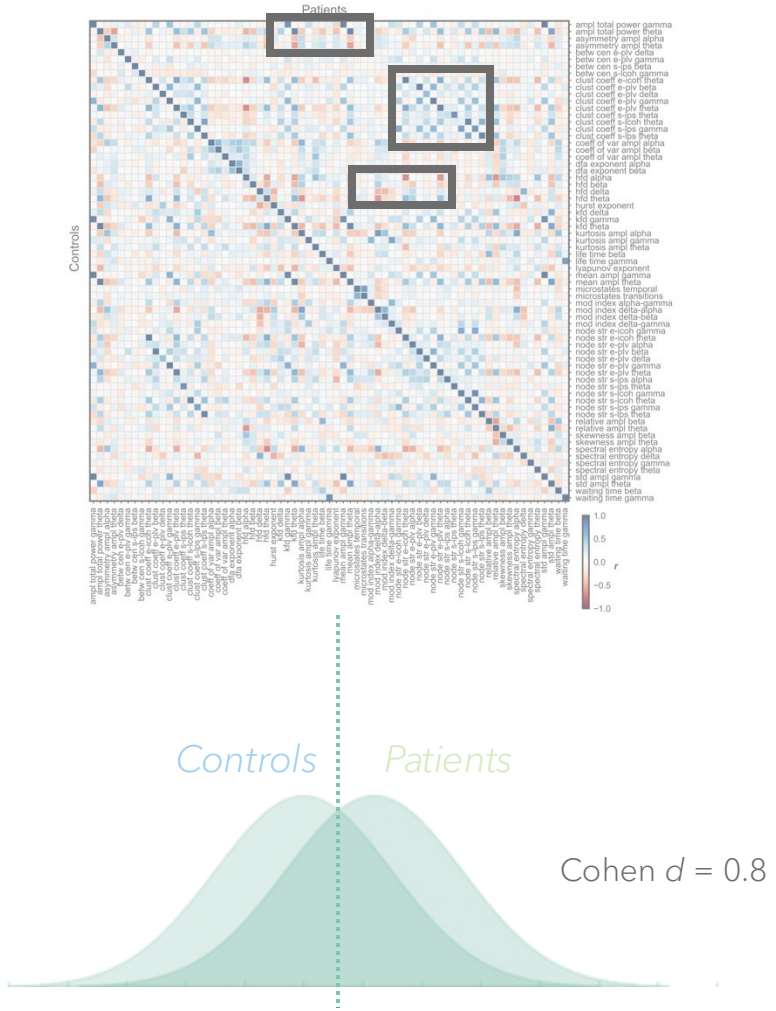
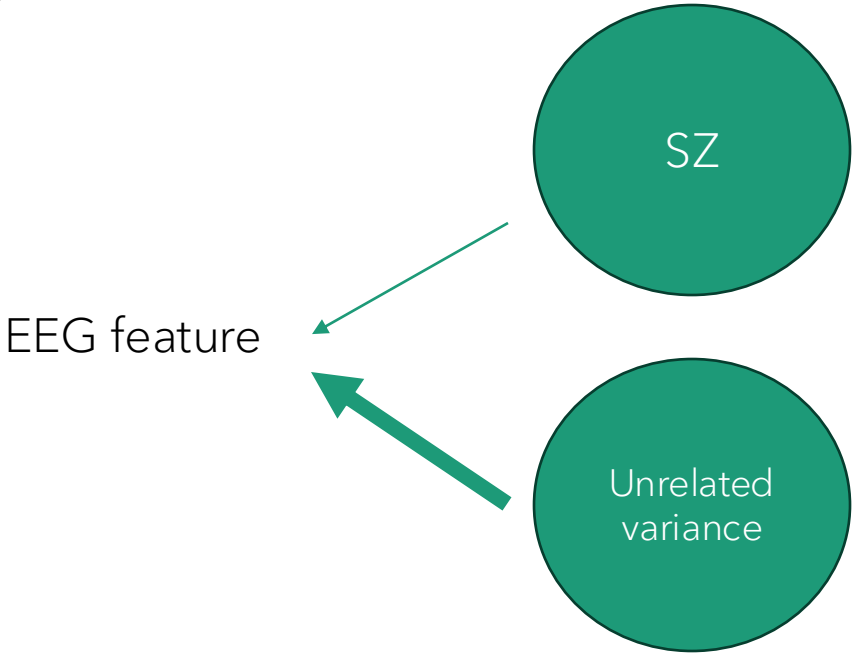


Idiosyncratic measures?

- The EEG features target a mechanism related with schizophrenia, but also other idiosyncratic aspects contributing to the variance
  - Comorbidities
  - By-products of the target mechanism
  - ….



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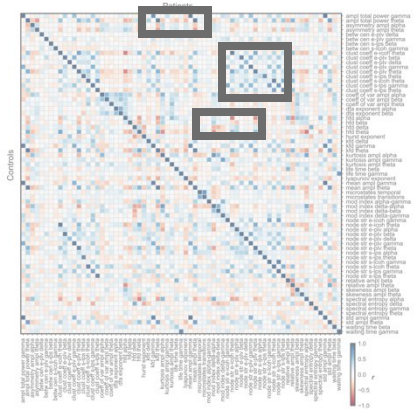
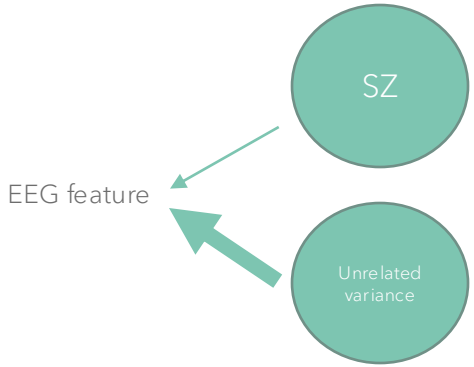
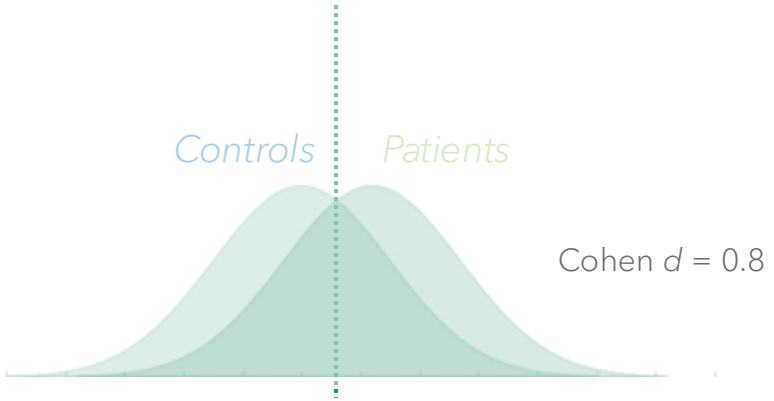


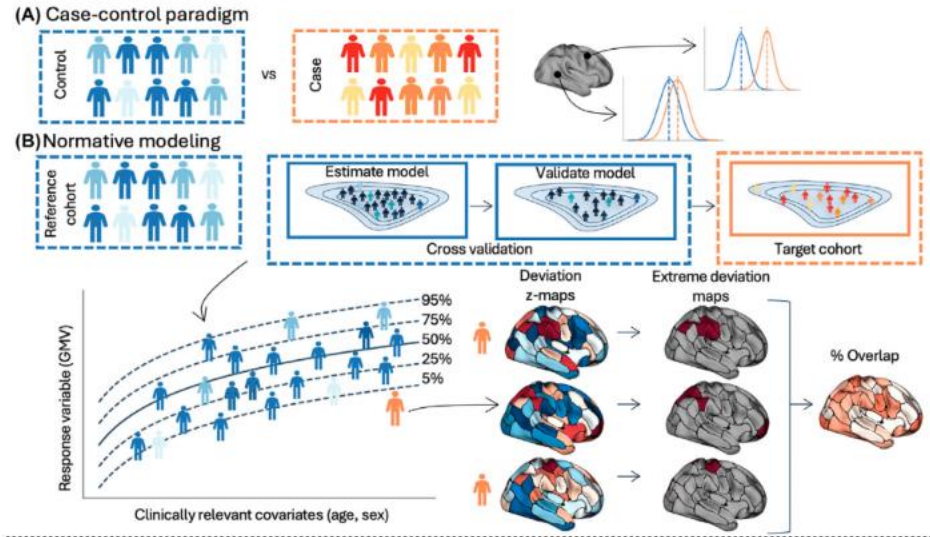




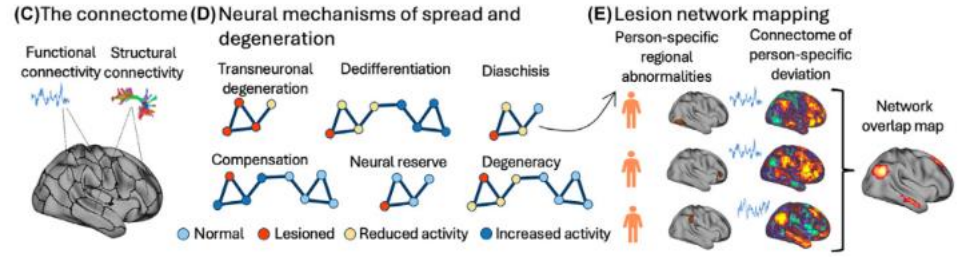
Heterogeneity

- Low correlations indicate multiple underlying factors
  - Different causes to the same disorder?
- What type of disorder is schizophrenia?
  - Additive?
  - Combinatorial?
- In this complex scenario, using one feature will have limitations

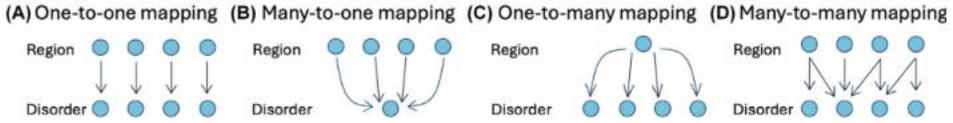
Problematic Assumption 1: The group mean is representative



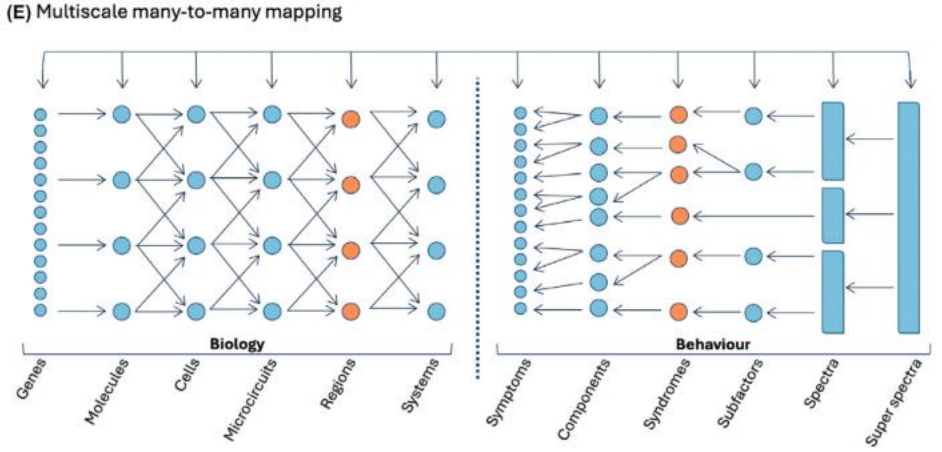
Problematic Assumption 2: Brain regions operate as isolated units



Problematic Assumption 3: One-to-one mapping



Problematic Assumption 4: Diagnostic categories are the appropriate phenotypic resolution

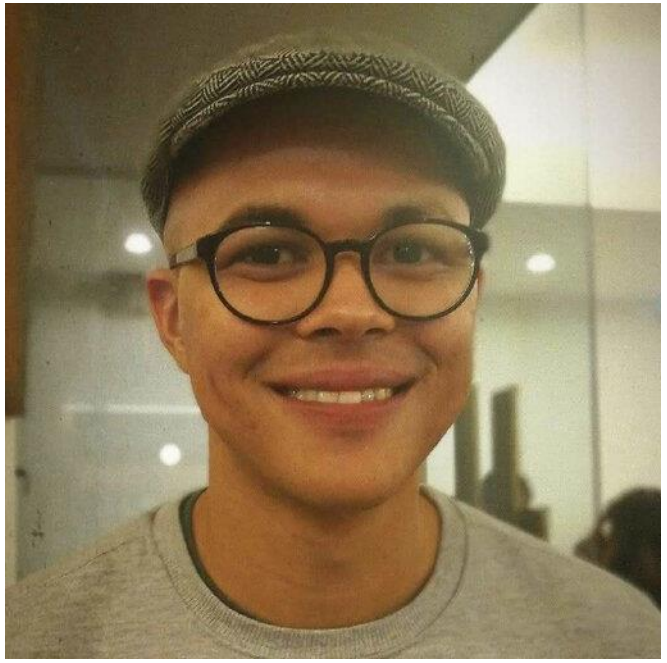


Segal et al., 2024

Conclusions

- Analyzing multiple features can help identify contributing factors to complex disorders
- There is not a single factor that explains neurophysiological deficits in schizophrenia
- Within subject studies can help understanding complexity
- Low correlations might indicate multiple causes
- Both approaches are needed to understand schizophrenia

Acknowledgements



Janir Ramos da Cruz

Eka Chkonia and Maya Roinishvili

Andreas Brand

Michael Herzog

Thanks for your attention