SOMIGLIANZE E DIFFERENZE TRA MODELLI MULTIVARIATI DI DEFICIT COGNITIVI E SOCIO-COGNITIVI NELLA SCHIZOFRENIA, NEL DISTURBO BIPOLARE E NEL RISCHIO CORRELATO

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Mind the gap: l'intervento precoce
tra continuità evolutiva, discontinuità diagnostiche e multiculturalità.

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Università degli Studi di Bari "Aldo Moro"

DISCLOSURE INFORMATION

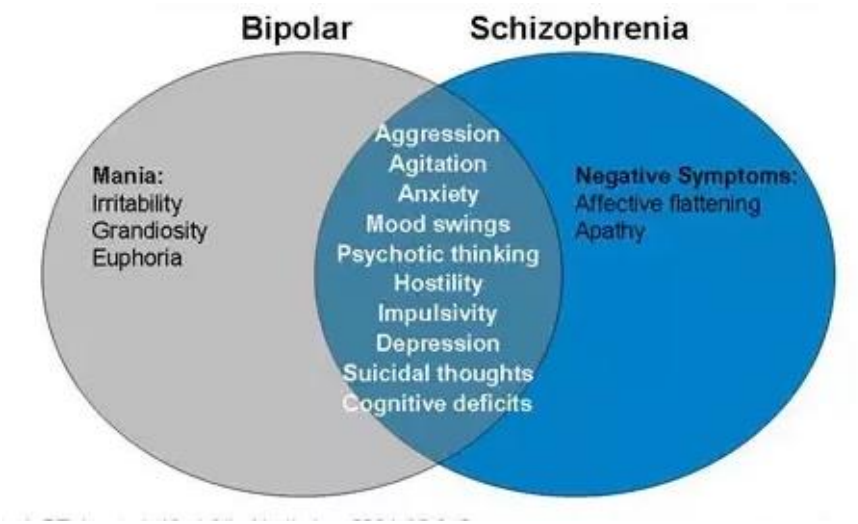
Alessandra Raio

Dichiaro che negli ultimi due anni non ho avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

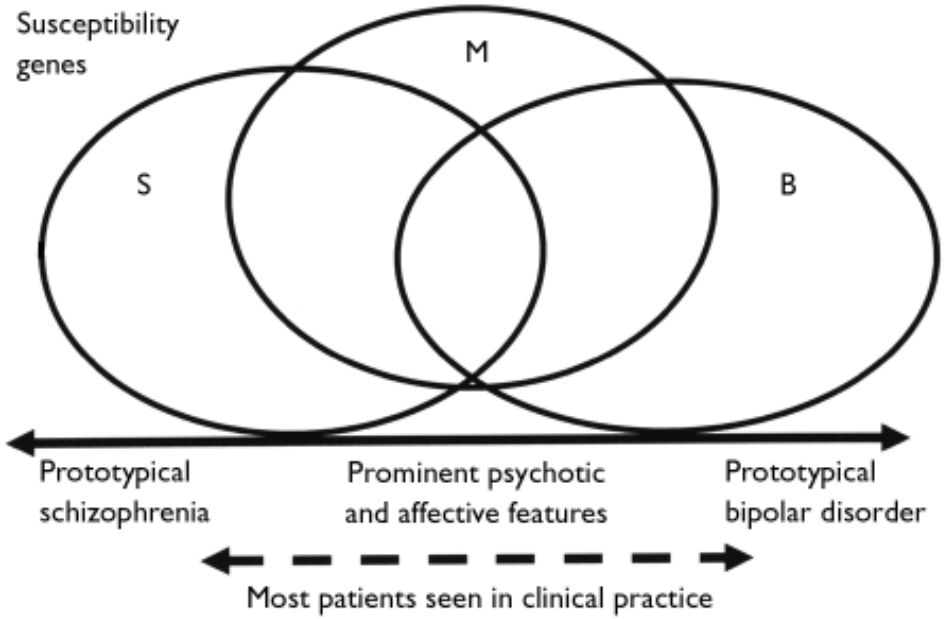
SCHIZOPHRENIA AND BIPOLAR DISORDER: FROM SEPARATION TO CONTINUITY

Despite the traditional nosological discrimination separating schizophrenia and bipolar disorder[1], cross-domain evidence suggests a quite large degree of overlap between the two disorders at multiple levels.

CLINICAL OVERLAP[2,3]



PARTIALLY SHARED GENETIC RISK[4,5]



THE EXTENDED CONTINUUM

PSYCHOTIC SYMPTOMS

Schizophrenia

Schizoaffective disorder
Psychotic symptoms with AND without depression/mania

Major Depressive Disorder / Bipolar disorder

WITH psychotic symptoms

Mostly depression / mania

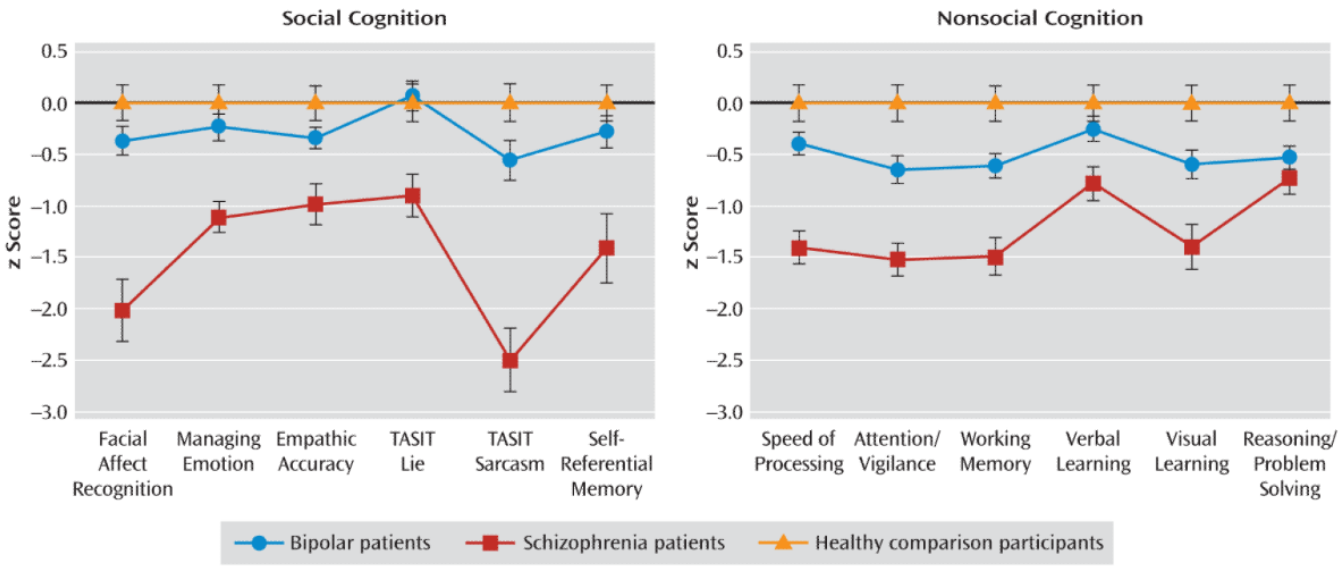
WITHOUT psychotic symptoms

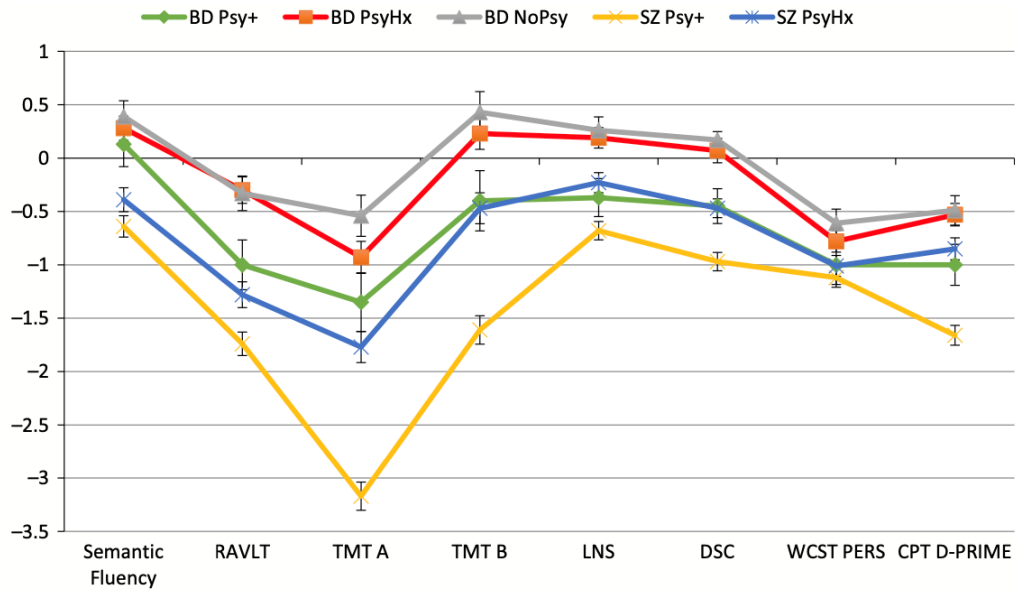
DEPRESSION/MANIA SYMPTOMS

1. American Psychiatric Association, 2013
2. Pearlsnon, 2015
3. Lake, 2010
4. Moskvina et al., 2009
5. Purcell et al., 2009

THE "QUANTITY-OR-QUALITY" DILEMMA

Among phenotypes in common between patients with schizophrenia (SCZ) and with bipolar disorder (BD), those related to cognitive and socio-cognitive impairments [6,7] play a key role, resulting crucially associated with both the diseases [8].





The most of univariate literature[9,10] is relatively consistent in showing **more quantitative (i.e., in terms of severity of impairments) than qualitative (i.e., in terms of differentially impaired domains) differences** between full-blown bipolar disorder and schizophrenia for what concerns the pool of typical cognitive and socio-cognitive alterations.

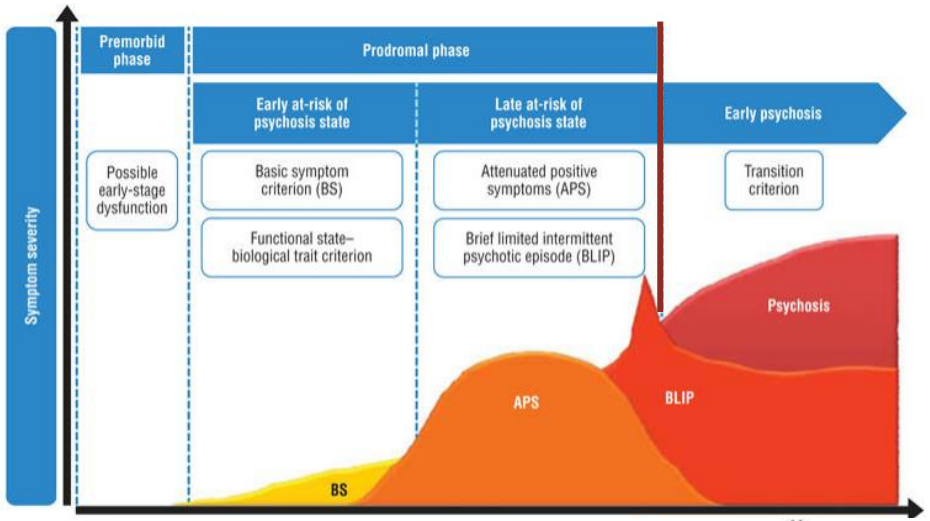
THE COMPLEXITY GAP (1): WHAT ABOUT THE INTERACTION BETWEEN COGNITION AND SOCIAL COGNITION?

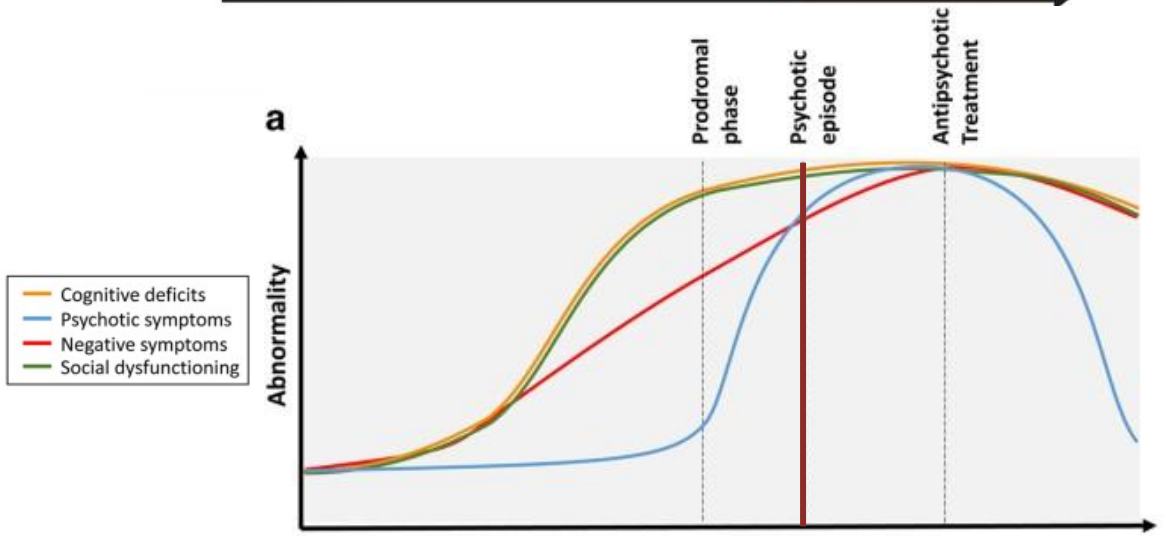
6. Bortolato et al., 2016
7. Bora & Pantelis, 2016
8. Jiménez-Lopéz et al., 2019
9. Daban et al., 2006
10. Reichengberg at al., 2009

BACK TO THE ORIGINS: THE EXTENDED RISK CONTINUUM

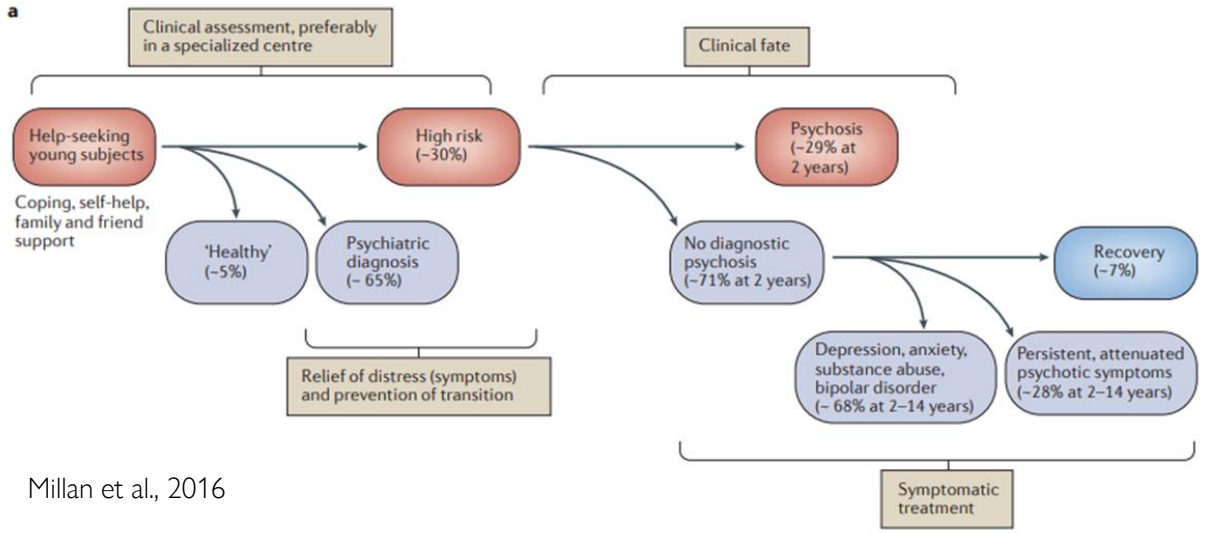
Subclinical signs identifying risk conditions for both psychosis and bipolar disorders are paralleled by similar (quantitatively and qualitatively) cognitive and socio-cognitive impairments[11,12,13]

Overlapping cognitive and socio-cognitive abnormalities in full-blown BD and SCZ as potential downstream manifestations of a common risk core...





THE HETEROGENEITY GAP (2)



Millan et al., 2016

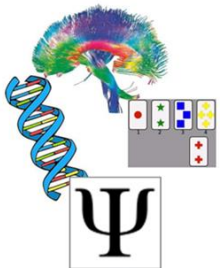
...described by highly heterogeneous susceptibility trajectories resulting in multiple clinical fates and outcomes.

11. Sheffield et al., 2018; 12. Bauer et al., 2018; 13. Lee et al., 2015

MIND THE GAPS: THE MACHINE LEARNING OVERCOMING CONTRIBUTION

MACHINE LEARNING (ML) TECHNIQUES ALLOW TO OVERCOME BOTH THE COMPLEXITY AND THE HETEROGENEITY GAPS BY DELIVERYING DATA-DRIVEN MODELS BASED ON DECISIONAL RULES

MULTIVARIATE



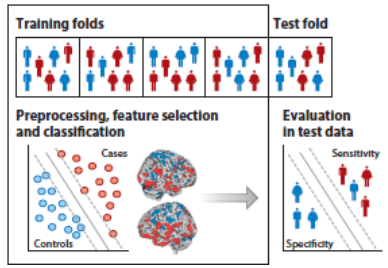
Identification of latent interactions between multiple domains (i.e. cognition, social cognition) and eligible markers of psychopatology (risk) from multiple predictors used as a unique multivariate information[14,15]

INDIVIDUALIZED

Results quantified at the single subject-level (rather than at the group-level only)[16]

GENERALIZABLE

Validation of the generated models on independent popoulations of individuals via internal and external cross-validation (CV) methods[16]



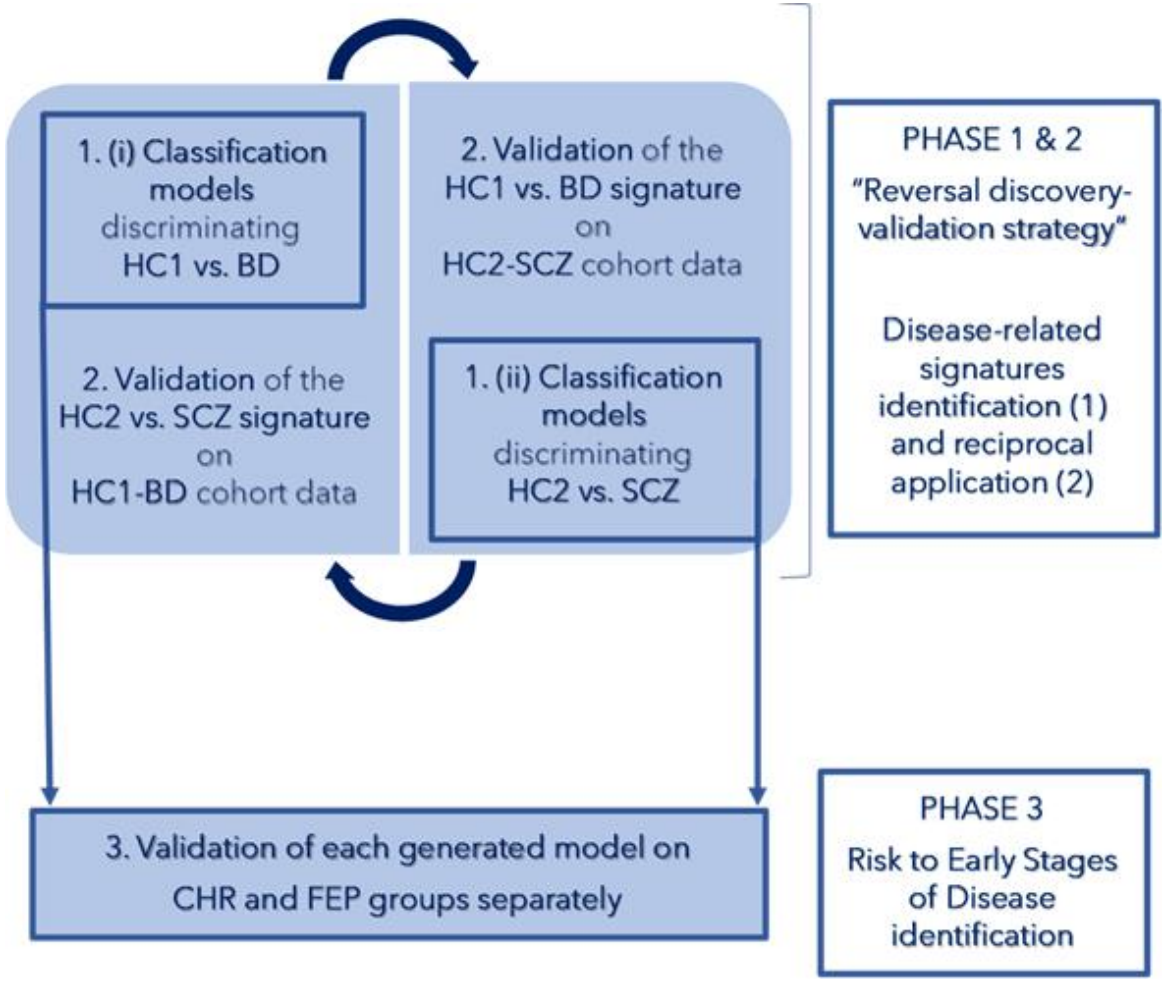
ML FEEDS RESEARCH: SUCCESSFUL IDENTIFICATION (AT FULL-BLOWN STAGES) AND GENERALIZATION (TO EARLY ONSET AND AT RISK CONDITIONS) OF INDIVIDUALIZED AND FINE-GRAINED PATTERNS OF COGNITIVE AND SOCIO-COGNITIVE ALTERATIONS

ML FEEDS CLINICAL PRACTICE: READY-TO-USE INFORMATION ABLE TO SUPPORT CLINICAL DECISION MAKING IN THE REAL-WORLD PRACTICE (EARLY DIAGNOSIS, PROGNOSIS, NON PHARMACOLOGICAL TREATMENT)

14. Kloppel et al., 2008; 15. Lao et al., 2014; 16. Dwyer et al., 2018

AIMS AND STUDY DESIGN

To identify profiles of cognitive and socio-cognitive similarities and differences between bipolar disorder and schizophrenia, also testing their prognostic relevance before the full-blown onset



1) To identify data-driven cognitive and socio-cognitive signatures of BD and SCZ at the single-subject level, furtherly investigating:

2) their trans-diagnostic relevance (VS. specificity for each diagnosis)

3) if the identified signatures were also relevant to risk conditions for these diseases or their early stages.

SAMPLE CHARACHTERIZATION AND MACHINE LEARNING PIPELINE

Table 1. Demographic and clinical characteristics of: (**A**) Healthy Controls (group 1) compared with Bipolar Disorder patients; (**B**) Healthy Controls (group 2) compared with Schizophrenia patients.

A. HC1-BD cohort	HC1 + BD (mean ± SD)	HC1 (mean ± SD)	BD (mean ± SD)	HC1 vs. BD (T/χ^2 [*p*-value])
Sample size	154	95	59	n.a.
Gender ratio (M/F)	66/88	36/59	30/29	1.99 [0.16]
Age	30.9 ± 11.7	26.57 ± 7.55	38.08 ± 13.66	−5.9 [<0.001*]
Socio-Economic Status	37.4 ± 17.4	41.25 ± 16.57	31.19 ± 17.06	3.6 [<0.001*]
Current IQ	102.2 ± 15.8	110.13 ± 11.54	89.32 ± 13.25	10.3 [<0.001*]
Premorbid IQ	113.5 ± 5.9	116 ± 2.70	109.47 ± 7.29	6.6 [<0.001*]
GAF total score	n.a.	n.a.	64.3 ± 6.2	n.a.
Lithium carbonate Equivalent dose	n.a.	n.a.	0.79 ± 0.39	n.a.
PANSS total score	n.a.	n.a.	48.6 ± 6.4	n.a.
YMRS total score	n.a.	n.a.	3.9 ± 1.3	n.a.
B. HC2-SCZ cohort	**HC2 + SCZ (mean ± SD)**	**HC2 (mean ± SD)**	**SCZ (mean ± SD)**	**HC2 vs. SCZ (T/χ^2 [*p*-value])**
Sample size	313	195	118	n.a.
Gender ratio (M/F)	117/136	88/107	89/29	26.24 [<0.001*]
Age	28.35 ± 8.12	26.40 ± 6.87	31.58 ± 8.99	−5.4 [<0.001*]
Socio-Economic Status	36.12 ± 17.54	39.37 ± 16.86	30.75 ± 17.40	4.3 [<0.001*]
Current IQ	96.96 ± 18.67	108.12 ± 10.57	78.63 ± 14.03	21.1 [<0.001*]
Premorbid IQ	112.36 ± 6.66	115.33 ± 3.36	107.46 ± 7.78	10.4 [<0.001*]
GAF total score	n.a.	n.a.	56.10 ± 8.89	n.a.
Chlorpromazine equivalent dose	n.a.	n.a.	118.76 ± 34.19	n.a.
PANSS total score	n.a.	n.a.	99.08 ± 26.55	n.a.

Table 2. Demographic and clinical characteristics of: [**A**] Clinical High-Risk individuals; [**B**] First Episode of Psychosis individuals.

A	Clinical High-Risk	ANOVA comparison between CHR-HC1-BD (F [*p*])	ANOVA comparison between CHR-HC2-SCZ (F [*p*])
Sample size	35	n.a.	n.a.
Gender ratio [M/F]	24/11	n.a.	n.a.
Age	19.80 ± 4.5	46.2 [<0.001*]	283.7 [<0.001*]
Socio-Economic Status	31.6 ± 16.6	8.2 [<0.001*]	10.5 [<0.001*]
Current IQ	87.4 ± 11.6	74.9 [<0.001*]	223.3 [<0.001*]
Premorbid IQ	107.4 ± 5.9	48.9 [<0.001*]	87.7 [<0.001*]
B	**First Episode of Psychosis**	**ANOVA comparison between FEP-HC1-BD (F [*p*])**	**ANOVA comparison between FEP-HC2-SCZ (F [*p*])**
Sample size	29	n.a.	n.a.
Gender ratio [M/F]	17/12	n.a.	n.a.
Age	22.4 ± 5.2	35.1 [<0.001*]	275.1 [<0.001*]
Socio-Economic Status	35.9 ± 17.1	6.6 [0.002*]	9.3 [<0.001*]
Current IQ	73.1 ± 15.5	111.2 [<0.001*]	259.9 [<0.001*]
Premorbid IQ	106.8 ± 6.1	49.4 [<0.001*]	88.2 [<0.001*]

MODALITY 1
COGNITIVE UNIMODAL CLASSIFIER
(52 FEATURES)

Phonologic and semantic fluency
Continuous Performance Task
Trail Making Test
Wechsler Memory Scale
Rey Auditory Verbal Learning Test
N-Back task (0,1,2 back)
Wisconsin Card Sorting Test

MODALITY 2
SOCIO-COGNTIIVE UNIMODAL CLASSIFIER
(37 FEATURES)

FEIT
(Facial Emotion Identification Test)
TASIT
(The Awareness of Social Inference)
MSCEIT
(Meyer-Salovey-Caruso Emotional Intelligence Test)

CLASSIFICATION ALGORITHM

Classification strategy
Support Vector Machine (LIBSVM)
11 C parameters
(0,0156 [first] -16 [last])

Number of modalities:
2
Cognition
Social cognition

Fusion strategies:
Stacking-based

CROSS VALIDATION FRAMEWORK

Double cycle, nested cross-validation

CV1 (inner cycle)
5 permutations, 10 folds

CV2 (outer cycle)
5 permutations, 10 folds

PREPROCESSING PIPELINE

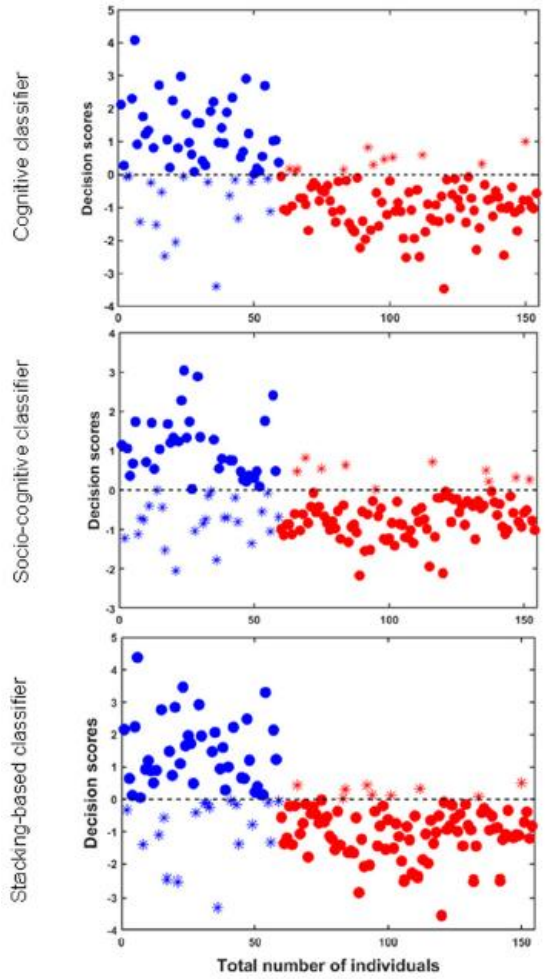
→ 0-1 scaling of data
→ k-Nearest Neighbor imputation
→ Partial correlations to regress out age and gender confounding effect

FEATURE ENGINEERING

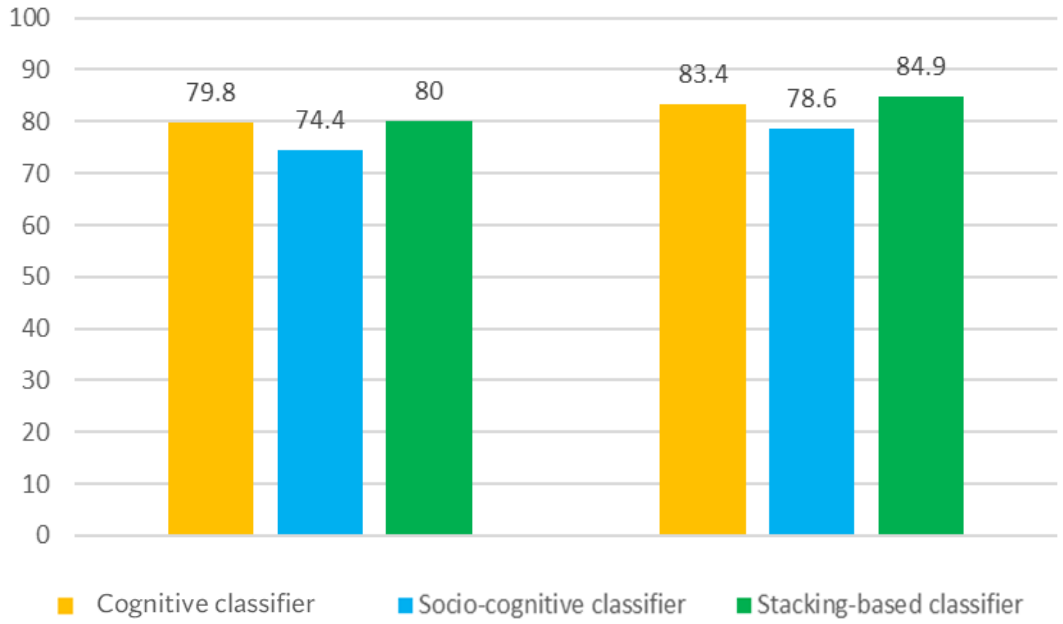
Wrapper-based procedures

(Forward greedy feature selection, 80% early stopping, each feature stepping)

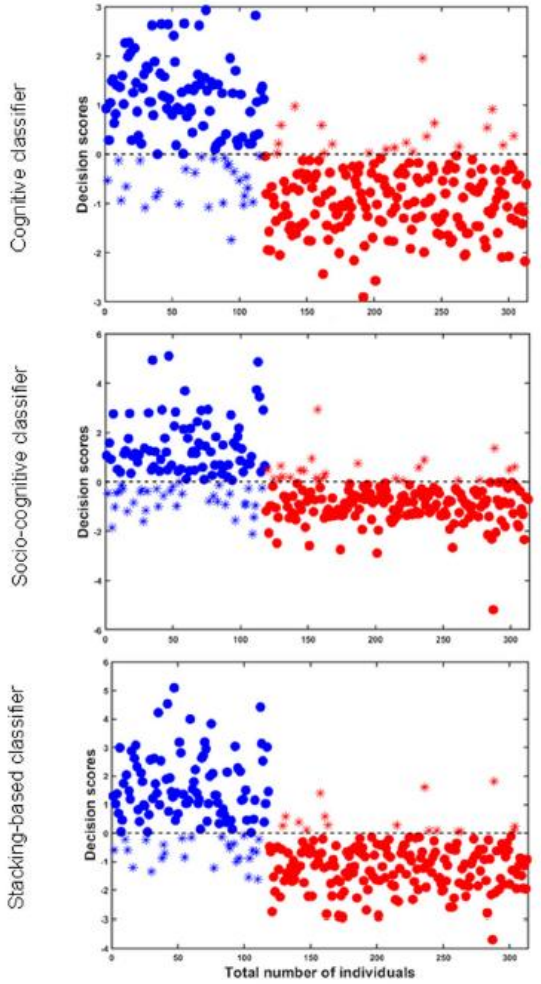
DISCOVERY UNIMODAL AND MULTIMODAL CLASSIFICATION ALGORITHMS
Between-cohorts performance comparison



CLASSIFICATION MODELS (Balanced Accuracy %)



In both the cohorts the multimodal classifier
(i.e., stacking-based model) performed better than the two unimodal classifiers

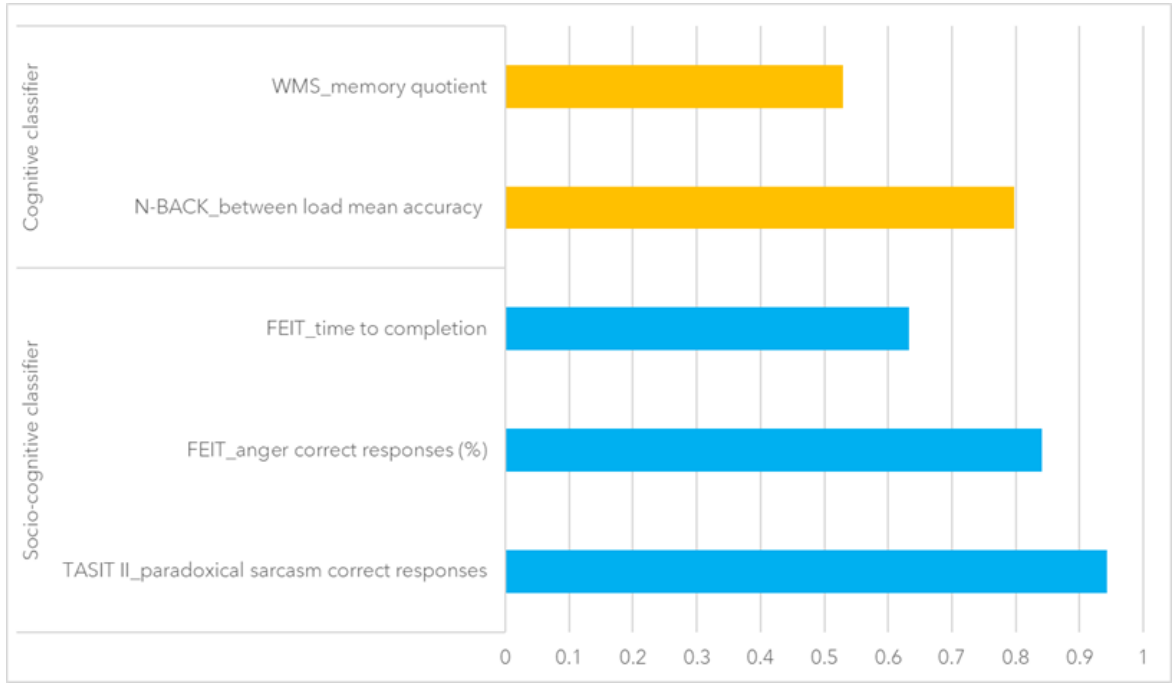


THE MULTIMODAL INFORMATION CONTRIBUTES TO BETTER DISCRIMINATE BETWEEN HEALTHY CONTROLS AND PATIENTS

WHAT KIND OF DEFICITS AT THE CORE OF EACH DISORDER?

Probability of each feature for being selected in the Machine Learning Cross-Validation framework for the cognitive and the socio-cognitive classifiers

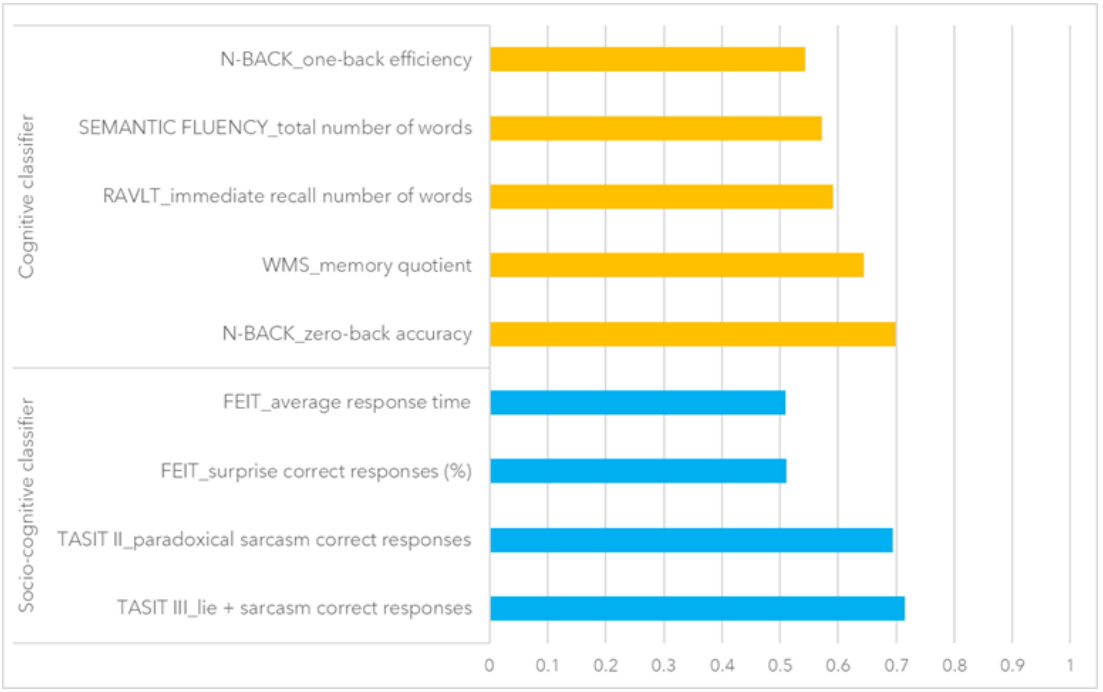
HC1-BD



COGNITION → dominance of **memory-related** core deficits

SOCIAL COGNITION
→ dominance of **emotion identification** core deficits

HC2-SCZ



COGNITION → broader pool of core deficits
(information processing + memory and learning + semantic fluency)

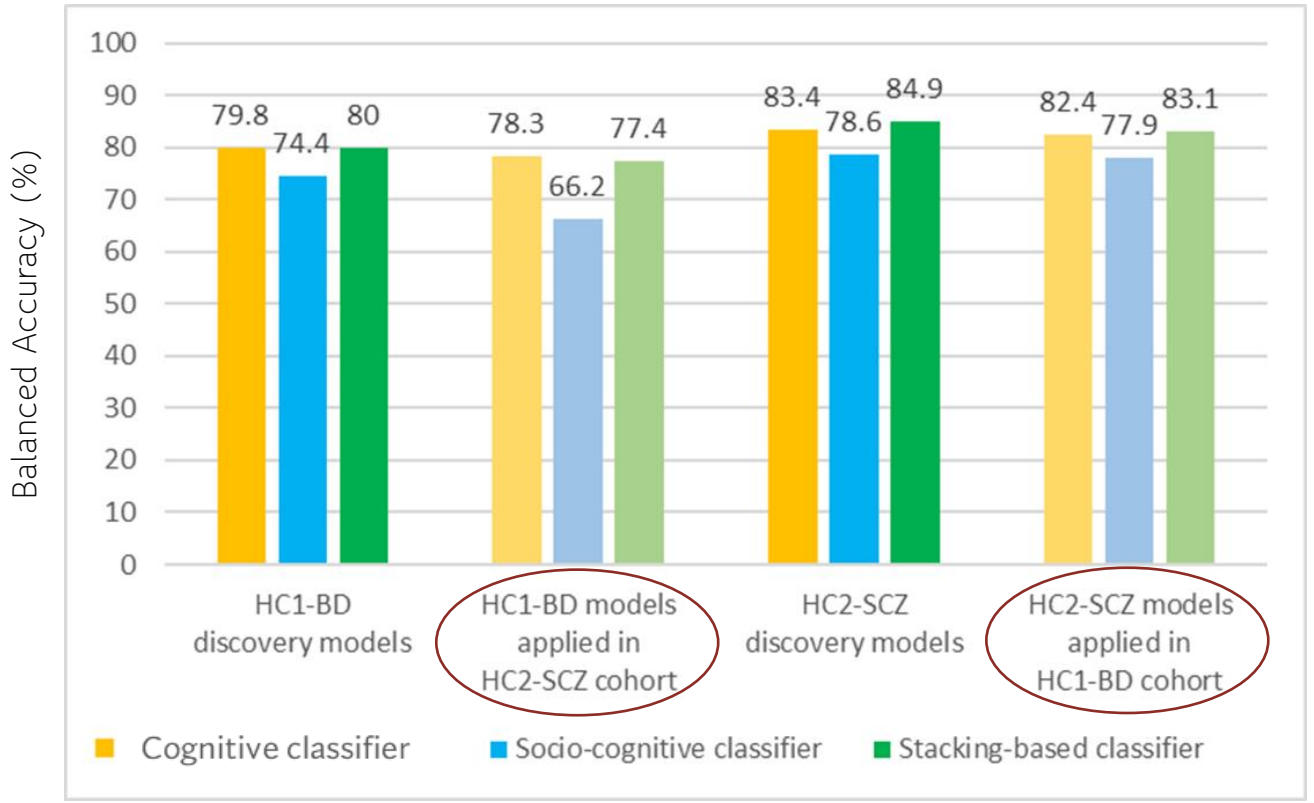
SOCIAL COGNITION → more balanced core deficits among basic and complex social inference and emotion identification

REVERSAL DISCOVERY-VALIDATION STRATEGY
Classification performance (2)

Reciprocal validation
of the signatures generated in
HC1-BD and HC2-SCZ cohorts

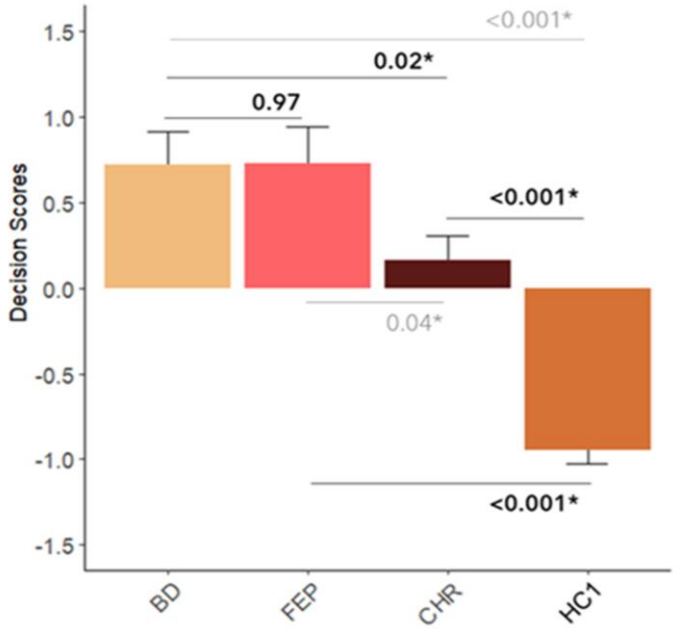
→ Despite the identification of some "core", diagnosis-related alterations, the high generalization of each model to unseen individuals with a different diagnosis proved the non-specificity of the overall bipolar and schizophrenia signatures

"Fade" bars represent the performance derived from the application of all the models generated in each discovery cohort on the data from the other one

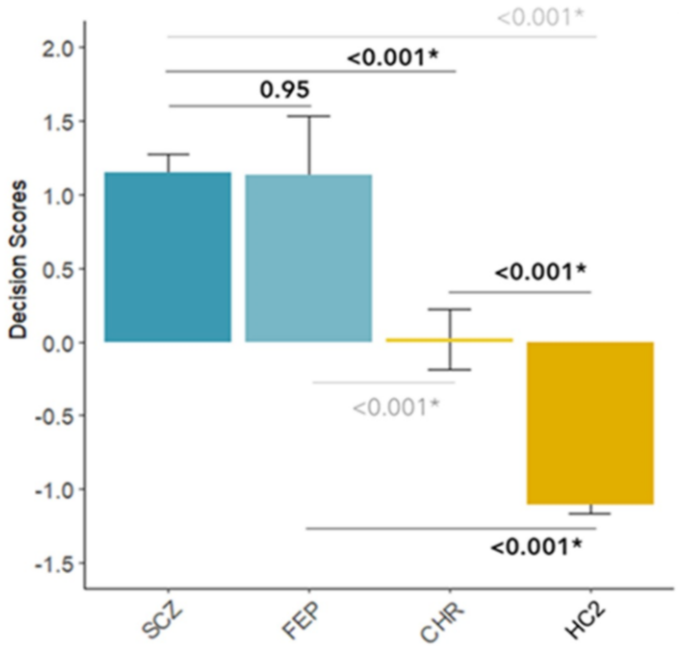


EXTERNAL VALIDATION ON INDIVIDUALS AT CLINICAL RISK OR AT FIRST EPISODE OF PSYCHOSIS

External validation
of the multimodal HC1-BD discovery model



External validation
of the multimodal HC2-SCZ discovery model



- BD-related and SCZ-related multimodal signatures generalized to early stages of disease irrespectively from diagnostic boundaries
- CHR may be affected by cognitive and socio-cognitive alterations, but such impairments may not be shaped as those present in full-blown schizophrenia or bipolar disorder yet

CHR = individuals at Clinical High Risk
HC1 = Healthy controls (group 1)
BD = patients with Bipolar Disoder
FEP = individuals at First Episode of Psychosis
SCZ = patients with Schizophrenia
FEP = individuals at First Episode of Psychosis
CHR = individuals at Clinical High Risk
HC2 = Healthy controls (group 2)

FINAL LANDMARKS AND CONCLUSIONS

1. Despite diagnosis-related **"hubs" of cognitive and socio-cognitive alterations** can be identified, full-blown bipolar disorder and schizophrenia share in both domains an overall common pattern of multi-domain impairments that should therefore be trans-diagnostically approached. For both the diseases, classification signatures' accuracy benefit from the combination of information from both the cognitive and the socio-cognitive domain (→ multimodal model bears the greatest amount of classification power)

→ effective remediation strategies for BD or SCZ individuals should be tailored both on these specific cognitive and socio-cognitive deficits at the core of each disorder, but anyway within an overall approach involving assessment and intervention also on less central alterations.

2. Our findings support the potential translation of such trans-diagnostic framework at earlier stages of diseases, but only after the disease onset and not when individuals are just at clinical risk.

→ our results are potentially relevant from a clinical perspective, as they provide ready-to-use information to refine individualized intervention focused on cognitive and socio-cognitive impairments for both the earlier and the chronic phases of the diseases.

GRAZIE PER L'ATTENZIONE

!

Schizophrenia

ARTICLE OPEN

Check for updates

Similarities and differences between multivariate patterns of cognitive and socio-cognitive deficits in schizophrenia, bipolar disorder and related risk

Alessandra Raio[1], Giulio Pergola[1], Antonio Rampino[1,2], Marianna Russo[1], Enrico D'Ambrosio[1,3], Pierluigi Selvaggi[1,2], Valerie De Chiara[1], Mario Altamura[4], Flora Brudaglio[5], Alessandro Saponaro[6], Domenico Semisa[7], Alessandro Bertolino[1,2], Linda A. Antonucci[1,8✉], Giuseppe Blasi[1,2,8✉] and the Apulian Network on Risk for Psychosis*