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Cognitive, Clinical, and Biomarker Correlates of Insight in Obsessive–Compulsive Disorder: preliminary results of a cross-sectional study

Scientific Disciplinary Sector(s)

Scientific Disciplinary Sector(s) PSICHIATRIA
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1. Introduction

1.1 Obsessive–Compulsive Disorder and Cognitive Performances

Obsessive–compulsive disorder (OCD) is a chronic, disabling psychiatric condition characterized by intrusive thoughts, images, or urges (obsessions) and repetitive behaviors or mental rituals (compulsions) intended to reduce distress or prevent feared outcomes.[1] Its lifetime prevalence ranges between 1 % and 3 %.[2] The disorder usually begins in adolescence or early adulthood and follows a waxing–waning course, imposing a major social, occupational, and emotional burden comparable to that of schizophrenia.[1] Even with optimal pharmacotherapy and psychotherapy, 20–30 % of patients remain treatment-refractory, with persistent intrusive symptoms and pervasive functional impairment.

Recent conceptualizations increasingly view OCD not merely as an anxiety-based syndrome but as a multilevel neurocognitive disorder, involving maladaptive loops between habit circuitry, metacognitive control, and social information processing.[1–3] This perspective broadens the traditional fronto-striatal framework to encompass social-emotional networks such as the amygdala, insula, and anterior cingulate cortex (ACC), which mediate both internal error monitoring and interpersonal inference.

In this framework, OCD can be interpreted as a disorder of cognitive control and performance monitoring, with robust evidence for deficits in response inhibition, cognitive flexibility, and set-shifting.[4,5] Electrophysiological studies consistently demonstrate enhanced error-related negativity (ERN) amplitudes localized to the Anterior Cingulate Cortex (ACC), reflecting hyperactive internal monitoring.[6] As Jansen et al. (2020)[1] emphasize, many of these same neural circuits underlie social cognition—including empathy and theory of mind (ToM)—suggesting that

cognitive inflexibility in OCD may extend from purely executive domains to navigating complex interpersonal milieu.

Farouk et al. (2025)[2] corroborate this view, reporting that patients exhibit reduced ToM and over-mentalization errors on the dynamic Movie for the Assessment of Social Cognition (MASC) test, implicating excessive attribution of intentions to others as a cognitive bias mirroring intrusive ideation. Such findings bridge executive and social dysfunction within a shared neural substrate.

Several prominent attempts have been made in characterizing OCD phenotypes, some focusing on the insight level, some others on comorbidities or on the main object of obsession or compulsion.[7,8] Neurodevelopmentally, early-onset cases show greater genetic loading and tic comorbidity, whereas later-onset forms may relate more to affective dysregulation and environmental triggers.[9] Functional MRI studies indicate that early-onset OCD involves stronger striatal hyperactivation, while adult-onset forms display greater prefrontal dysconnectivity.[10] In this context, translational biomarkers such as BDNF may be particularly valuable to study, as these trajectories may differentially affect neurotrophic signaling and influence synaptic refinement during adolescence and adulthood.[11]

Social cognition encompasses the perception, interpretation, and regulation of socio-emotional cues, indispensable skills for adaptive social functioning.[12] Multiple studies now demonstrate that OCD entails deficits in social cue perception, especially in recognizing facial expressions of disgust, anger, and fear.[1,13] These deficits mirror the symptom-specific activation of the insula during contamination-related tasks and link disgust sensitivity to contamination obsessions.[14,15]

Neuroimaging data converge on aberrant recruitment of the amygdala, insula, and ACC during emotional and social inference tasks, regions jointly considered part of the social brain.[16] As Jansen et al. (2020)[1] and Farouk et al. (2025)[2] both note, these same structures are linked to ToM processing and emotional self-referential evaluation, reinforcing the notion that social dysfunction in OCD is not epiphenomenal, but intrinsic to its pathophysiology.

Dynamic-stimulus paradigms (e.g., Movie for the Assessment of Social Cognition - MASC) further suggest that OCD patients display over-mentalization—excessively complex or inaccurate inferences about others' intentions—rather than under-mentalization, paralleling the ruminative over-attribution characteristic of obsessions.[2] This highlights a paradoxical combination of hyper-reflectivity and cognitive rigidity within interpersonal contexts.

Insight variability in OCD has profound implications for both prognosis and cognition.[17] Poor-insight subtypes exhibit stronger conviction in obsessive beliefs and diminished self-reflective awareness. Jansen et al. (2020)[1] link this to ToM dysfunction: low-insight patients perform worse on mental-state reasoning, supporting the idea that metacognitive inflexibility may have significant overlap areas with impaired social inference.

Neuroimaging and electrophysiological evidence indicate that over-monitoring and doubt in OCD arise from aberrant coupling between error-detection and affective-evaluation circuits. Studies show that exaggerated activity in the ACC and orbitofrontal cortex (OFC) during performance monitoring tasks is accompanied by increased functional connectivity with limbic regions such as the amygdala.[6,18,19] This fronto-limbic hyperconnectivity sustains persistent internal "error signals" ("something is wrong") and enhances the salience of negative self-appraisal and social disapproval cues ("others disapprove"), thereby promoting reassurance seeking and compulsive checking.[20,21] Collectively, these findings support the view that metacognitive self-monitoring abnormalities in OCD are rooted in dysregulated integration between cognitive-control and emotional-valuation systems, linking error processing, anxiety, and interpersonal sensitivity within a unified fronto-striatal–limbic framework.

1.2 Neurobiological correlates for OCD: BDNF and inflammation

Numerous investigations have documented significantly reduced peripheral brain-derived neurotrophic factor (BDNF) levels in individuals with obsessive–compulsive disorder (OCD) compared with healthy controls.[22,23] Converging mechanistic work indicates that BDNF is a key regulator of cortico-striatal synaptic plasticity and learning; in OCD-relevant models, abnormalities in these fronto-striatal loops are central to maladaptive habit formation and impaired

extinction.[20,24] Taken together, BDNF dysregulation provides a biologically plausible substrate for reduced plasticity within cortico-striatal circuits that sustain compulsive behaviors and hinder extinction of obsessional responses. Meta-analyses show normalization of serum BDNF following successful SSRI treatment or cognitive-behavioral therapy,[22,25] consistent with restored neuroplastic homeostasis. Among the others, BDNF has been proposed as a possible modulator in emotion recognition and social learning, potentially linking molecular plasticity with ToM performance. Animal models demonstrate that hippocampal and prefrontal BDNF depletion impairs social novelty recognition and emotional flexibility,[26] therefore, variation in BDNF may reflect central social-cognitive efficiency.

1.3 Sleep, neuroplasticity and cognitive flexibility

An additional layer of complexity may be added by the potential association between OCD and sleep problems[27] and the interaction between sleep and cognition.[28] Sleep and BDNF are reciprocally regulated. Contemporary reviews show that sleep loss is associated with reductions in circulating BDNF, whereas sleep restoration is linked to up-regulation of BDNF in plasticity-relevant circuits (hippocampus, cortex).[29,30] Meta-analytic evidence indicates that adults with insomnia disorder exhibit lower peripheral BDNF than good sleepers.[31] Case-control and population data further suggest that subjective insomnia may be associated with BDNF and may be related to symptoms burden,[32] and observational studies report a negative association between insomnia and BDNF concentrations.[33] Together, these data support a model in which insomnia down-tunes neurotrophic tone, potentially constraining cognitive flexibility and emotional recalibration that depend on BDNF-mediated plasticity.

The role of peripheral BDNF extends far beyond the central nervous system. Kermani et al 2018[34] demonstrated that BDNF and its receptor TrkB are expressed in cardiomyocytes, endothelial cells, and vascular smooth muscle cells, where they modulate angiogenesis, contractility, and repair following ischemic injury. These peripheral actions imply that serum BDNF variations may reflect vascular plasticity and endothelial health, both of which contribute to cognitive and affective functioning. Indeed, local BDNF signaling in the cardiovascular system influences microvascular

integrity and cerebral perfusion, suggesting a mechanistic bridge between somatic health and cognitive performance.

Complementary findings from Konturek et al.[35] highlight the involvement of BDNF in gut–brain interactions, specifically within the context of irritable bowel syndrome (IBS). Their study described BDNF mRNA and protein expression in human colonic tissue, correlating with symptom severity and sex-specific differences. This supports the notion that peripheral BDNF may participate in visceral sensory processing and stress responsivity, potentially contributing to the somatic and affective symptom clusters observed in OCD and related anxiety disorders. The gut's enteric nervous system, richly innervated and responsive to BDNF, can influence central emotional circuits through vagal and inflammatory pathways, illustrating a bidirectional brain–gut–immune axis relevant to neurocognition.[36] At systems level, the neurovascular and neuroimmune roles of BDNF[34] suggest that cognitive and emotional rigidity in OCD may also have somatic correlates, including altered autonomic and vascular responses to stress. Persistent sympathetic arousal and endothelial dysfunction—partly driven by inflammatory cytokines—could reduce cerebral perfusion or oxygenation in fronto-striatal regions, further impairing metacognitive efficiency. In both central and peripheral tissues, BDNF exists in two biologically active forms—proBDNF and mature BDNF (mBDNF)—that act on distinct receptors (p75^NTR^ and TrkB, respectively) and produce opposite effects: proBDNF tends to promote apoptosis and synaptic pruning, whereas mBDNF supports neuronal survival and long-term potentiation.[37]

A substantial proportion of peripheral BDNF (over 90%) is stored in platelets, where it resides in both α-granules and the cytoplasm.[37] Upon platelet activation, BDNF is released into the circulation and typically accounts for roughly 30–40% of total platelet BDNF, suggesting that platelet reactivity can markedly influence measured serum concentrations. This observation is crucial, since psychiatric and inflammatory conditions are associated with both altered platelet function and changes in peripheral BDNF, potentially confounding biomarker interpretation. For example, platelet activation through thrombin or collagen stimulation can lead to selective release of α-granule BDNF, paralleling secretion patterns of serotonin and platelet factor 4 (PF4), which are themselves linked to mood and cognitive processes.[37]

The gut-derived BDNF alterations observed in Irritable Bowel Syndrome (IBS)[35] provide a

parallel model: chronic stress and altered BDNF expression in peripheral tissues correspond to visceral hypersensitivity and cognitive–emotional dysregulation, underscoring the potential for shared pathophysiological pathways across different systems.[38]

This element may serve as an empirical and reasonable bridge for physiology and psychopathology to converge, along with a possible rationale for evaluating peripheral BDNF in relation to psychopathological states.

1.4 Integrative Framework and Study aims

Integrating neurocognitive, social, and biological perspectives, obsessive–compulsive disorder (OCD) may be conceptualised as a disorder of maladaptive neuroplasticity within socio-emotional networks. Intrusive cognitions, hyperresponsibility, and rigid control behaviors not only tax executive resources but also may contribute to distorting self–other mentalizing processes.[1,2] Such dysfunctions may stem from impaired fronto-striatal modulation of salience and prediction error signals, mediated by aberrant plasticity mechanisms involving BDNF and inflammatory mediators.

BDNF may serve as a key molecular substrate linking synaptic remodeling to cognitive–affective flexibility. In line with what has been eloquently reported by Serra-Milas et al,[2] disturbances in the regulation of proBDNF/mBDNF balance may disrupt the fine-tuning of excitatory–inhibitory dynamics, compromising the capacity for flexible updating of beliefs—an essential component of both cognitive control and insight.

BDNF has been investigated in the past as a possible candidate biomarker of OCD, with the val66met variant in the phenotypic expression of obsessive–compulsive disorder, the Val66Val genotype and the Val66 allele with sexual/religious obsession and the Met66Met with an older age of onset.[39] To our knowledge, fewer studies have explored the potential of BDNF as a translational biomarker for other subtypes, such as Poor-insight OCD (OCDPI). Hypothetically, considering the described relationship between insight and cognition in OCD,[40] and that BDNF has already been shown to be associated with insight level in OCD,[41] replication studies may aim at confirming this association and also at possibly describing possible underlying mechanisms.

By incorporating platelet-derived neurotrophin biology,[37] vascular–endothelial mechanisms,[34] and gut–brain modulation,[35] sleep patterns[30] this framework points to BDNF as a translational biomarker within a multidimensional model where cognition, psychopathology, and sleep physiology coalesce through shared plasticity pathways. Such an integrating view could advance our understanding of the field from descriptive symptomatology toward mechanistically informed stratification, fostering personalised interventions—e.g., cognitive remediation combined with anti-inflammatory or neurotrophic-enhancing strategies (e.g., exercise, selective TrkB agonists).

Inflammatory markers such as TNF-α and C-reactive protein (CRP) further interact with neurotrophin systems, influencing synaptic plasticity and motivational states.[36] Elevated cytokines can suppress BDNF transcription or alter its receptor sensitivity, creating a neuroinflammatory milieu detrimental to learning, attention, and emotion regulation. Arguably, a joint assessment of BDNF and selected biomarkers such as TNF-α and CRP may thus offer a more integrative view of neuroplastic and immune homeostasis, enabling detection of bio-clinical phenotypes that transcend traditional diagnostic categories.
Inflammatory cytokines (TNF-α, CRP) exert modulatory effects on BDNF transcription via NF-κB and glucocorticoid pathways.[36] Elevated inflammation can suppress BDNF signaling and impair synaptic efficiency, linking systemic immune tone to cognitive outcomes. Arguably, sleep deprivation can further interact with BDNF pathways by promoting a persistent inflammatory state in addition to the direct effects already reported above.[42]

The combined evaluation of BDNF, TNF-α, CRP, and sleep thus provides a multidimensional biomarker framework to interpret cognitive variability within and across OCD subtypes.

By mapping cognitive heterogeneity onto biological parameters, this framework supports precision stratification within OCD. Integrating BDNF and sleep variables into analyses may, in theory, allow identification of patients whose cognitive impairments are neuroplastic-state-dependent rather than trait-cognitive. Meanwhile, incorporating insights, psychopathology, and cognitive measures may further broaden our understanding of this complex interaction.

Considering the foregoing, the current study leverages BDNF as both a molecular marker of neurocognitive plasticity and an index of systemic stress–immune adaptation. Its measurement alongside TNF-α and CRP can assist in disentangling trait-like neurotrophic profiles from state-dependent inflammatory responses, clarifying whether cognitive impairments in OCD reflect intrinsic neurobiological vulnerability or secondary physiological modulation.

With the present project we aim at delineating subtype-specific couplings between symptoms, insight, social cognition, sleep architecture, and peripheral biomarkers in OCD, and to identify low-dimensional axes that best explain this heterogeneity. Furthermore, we will explore potential interaction between psychopathology, sleep architecture, subjective sleep quality and the selected biomarkers levels.

The proposed approach aligns with current translational initiatives that emphasise multilevel, dimensional models—from molecules to social function. Ultimately, clarifying how BDNF, sleep, and social cognition interact may further advance our understanding of the underlying mechanisms.

2. Materials and methods

2.1 Data Preprocessing

The dataset used in this study comprises several types of information: socio-demographic data, neurocognitive and psychometric test results, polysomnography parameters, and blood assay values. For quantitative analyses, socio-demographic variables underwent a series of transformations and encodings to ensure homogeneity and compatibility with the statistical and

computational procedures adopted.

2.1.1 Encoding and Transformation of Socio-Demographic Variables

The main preprocessing steps applied to the original dataset were as follows:

- Sex: recoded into a binary format, assigning 0 to male and 1 to female participants.
- Psychiatric comorbidities: presence or absence represented by a binary variable (1 = present; 0 = absent).
- Other comorbidities: all distinct clinical conditions present in the sample were identified. For each condition, a new column was created in the dataset with binary values indicating the presence (1) or absence (0) of the specific condition for each participant.
- Geographic origin: excluded from the analyses as it was not relevant to the study hypotheses.
- Weight and height: combined to obtain Body Mass Index (BMI), calculated as:
  BMI = weight (kg) / height (m)^2
- Educational history: the qualitative variable describing the educational pathway was converted to a numeric format, expressing the education level as total years of schooling.
- Ethnicity of the patient and parents: excluded from the analyses because these variables were constant across the entire sample.
- Pharmacological treatment: the agents listed in the dataset were grouped into four main therapeutic macro-categories: 1) antidepressants, 2) antipsychotics, 3) sedatives, 4) mood stabilizers. For each category, a binary variable was created (1 = use; 0 = no use), indicating whether medications belonging to that class were present. We decided not to include in the analysis the prior medication history as this was considered no in line with the analytical objectives of the present study.

2.1.2 Neurocognitive Tests

Only T-scores were considered for neurocognitive tests, as they are standardized and comparable

across participants.

In the present study we employed the MATRICS Consensus Cognitive Battery (MCCB).[43] Originally developed for schizophrenia research, the MCCB provides standardized T-scores and percentiles across seven domains:

1. Speed of Processing
2. Attention/Vigilance
3. Working Memory
4. Verbal Learning
5. Visual Learning
6. Reasoning and Problem Solving
7. Social Cognition.

Both percentiles and T-scores were analyzed to capture linear and nonlinear effects across the performance spectrum. Domain MCCB Subtest Primary Measure 1. Speed of Processing Trail Making A, BACS Symbol Coding, Category Fluency Completion time / correct responses 2. Attention/Vigilance Continuous Performance Test – Identical Pairs d' (signal detection index) 3. Working Memory Letter-Number Span, WMS-III Spatial Span Total correct 4. Verbal Learning Hopkins Verbal Learning Test–Revised Total recall (HVLT-R) 5. Visual Learning Brief Visuospatial Memory Test–Revised Total recall 6. Reasoning/Problem Solving NAB Mazes Total correct 7. Social Cognition MSCEIT Managing Emotions Total correct

Psychometric Tests

Psychometric tests were administered separately to adults and to children/adolescents. For analysis purposes, only tests administered in both populations were considered to allow consistent and meaningful comparisons.

Adult population.

In adults, obsessive–compulsive symptom severity were evaluated using the Italian version of the Yale–Brown Obsessive–Compulsive Scale, Second Edition (Y-BOCS-II). The Brown Assessment of Beliefs Scale (BABS), a semi-structured clinician-rated interview composed of

seven items exploring conviction, perception of others' views, and ability to challenge one's own beliefs, will be administered to quantify the level of insight related to obsessive thoughts.

Pediatric population.

In the pediatric cohort, symptom severity were measured using the Italian version of the Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS). Behavioral and affective functioning will be evaluated with the Italian version of the Child Behavior Checklist (CBCL 6–18). Insight into obsessional beliefs was assessed with the Brown Assessment of Beliefs Scale—Adolescent version (BABS-A).

Sleep quality.

Across both age groups, subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), which evaluates seven domains: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) use of hypnotic medication, and (7) daytime dysfunction.

Whole sample.

Sociodemographic, personal, and familial information were collected for all participants, including: (1) participant ethnicity, (2) psychiatric comorbidities, (3) medical comorbidities, (4) paternal age at birth, (5) maternal age at birth, (6) self-reported socioeconomic status (three-level scale), (7) education level, (8) paternal ethnicity, (9) maternal ethnicity, (10) family history of psychiatric disorders, (11) family history of suicidal behaviors, and (12) lifetime history of substance use disorders.

2.1.3 Polysomnography and Blood Analyses

Polysomnography measures were obtained from a homogeneous subsample, meaning that at least one participant was present for each diagnosis. All available measurements were included in the subsequent analyses.

Blood assay data were treated analogously to polysomnography data: all collected measurements were included in the analysis, given the completeness and homogeneity of the subsample. The

only exception concerned IL-1β (pg/5 μL), which was non-informative (no variability in the sample).

The final dataset used for analyses can therefore be represented as a matrix in which rows correspond to individual patients and columns represent the set of variables selected and transformed as described above

2.2 Statistical Analysis

2.2.1 Normalization and Group Comparisons

Blood biomarkers (BDNF, CRP, TNF-α) were log-transformed to reduce distributional skewness and attenuate the influence of extreme values, which are frequently observed in such biological measures. Specifically, a $\log(x + 1)$ transformation was applied to each value to preserve zeros and avoid issues with the logarithm's definition. Variables were then standardized using z-score normalization with scikit-learn's StandardScaler (Python). This centered each variable to mean 0 and scaled it to unit standard deviation, enabling comparisons across variables with different units and ensuring balanced contributions to subsequent statistical analyses.

The distribution of log-transformed data was assessed using the Shapiro–Wilk test to verify normality within each diagnostic group.

Where significant deviations from normality were present, between-group differences were analyzed using nonparametric tests: Kruskal–Wallis as an omnibus test to compare all groups simultaneously. When significant, pairwise comparisons were conducted using the Mann–Whitney U test with multiple-testing correction via False Discovery Rate (FDR).

All p-values from pairwise comparisons were displayed in heatmaps, highlighting significant contrasts ($p < 0.05$) to clearly visualize differences between diagnostic groups. This procedure allows us to compare variables with non-Gaussian distributions and different measurement units.

This phase performs descriptive statistical analyses to characterize the distribution of variables in the dataset and to explore relationships among key clinical, neurocognitive, and demographic parameters.

2.2.2 Dimensionality Reduction and Classification

Subsequently, a machine-learning classification model will be developed to classify patients based on the available variables. The goal is to assess the predictive ability of the collected data in discriminating among different diagnostic categories, identifying variables with the highest informational contribution.

The dataset was split into two independent subsets: one for model training and the other for testing, to evaluate performance in terms of accuracy, sensitivity, specificity, and the potential risk of overfitting.

2.3 Challenges and Proposed Solutions

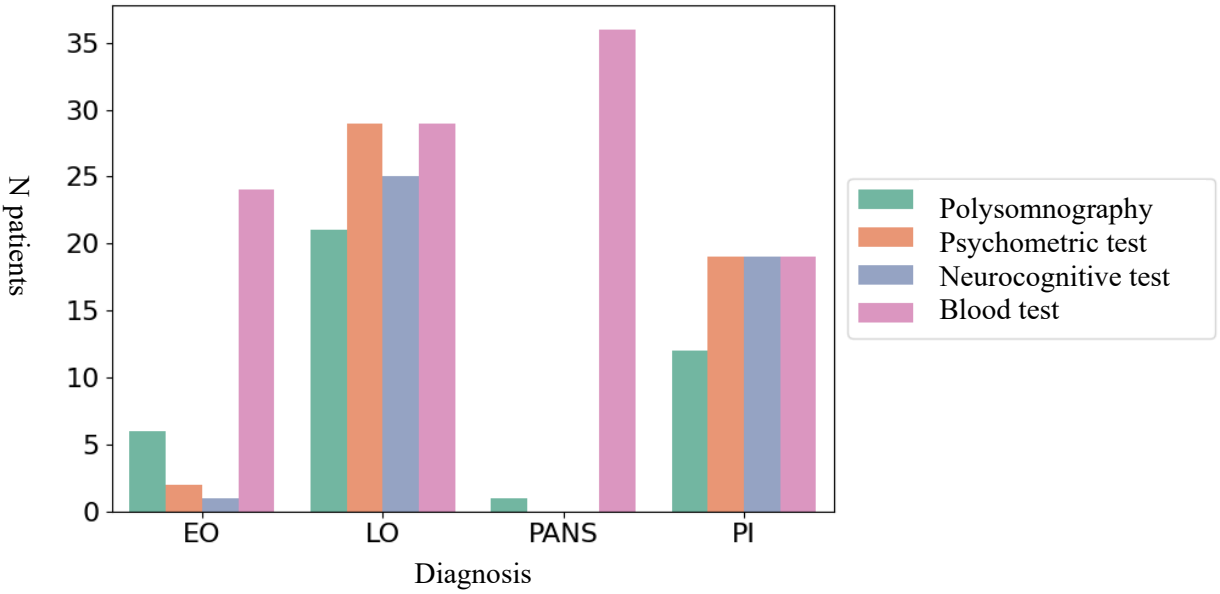

Figure 1. Bar chart for relevant tests and sample divided based on diagnostic subgroup.

As shown by the bar plot (number of patients, by diagnosis, included in each test battery), there are missing not at random (MNAR) data. In other words, some diagnostic categories are underrepresented or entirely absent in specific measurement sets due to differing selection criteria

or experimental conditions.

In particular, the PANS group is most affected: psychometric and neurocognitive test data are entirely missing for these patients, and for polysomnography only a single patient is available—insufficient for any statistically meaningful consideration.

To proceed with training and testing a regression model, the dataset must be as balanced as possible and free from structural biases that could lead to overfitting.

Overfitting occurs when a model learns overly specific characteristics of the training sample, adapting to random or non-generalizable patterns. For example, suppose two diagnostic categories are heavily imbalanced by age (e.g., all adults in one group and all minors in the other). In that case, the model may use age as the main classification criterion. The model would then distinguish diagnoses based on age—a variable not truly discriminative—instead of the clinical features of interest.

To reduce this risk, two alternative strategies can be adopted:

- Limit the analysis to the better-represented categories—i.e., adult patients belonging to the LO and PI groups—thus ensuring a more homogeneous and numerically balanced sample.
- Retain the entire sample, including all diagnostic categories, but exclude psychometric and neurocognitive tests, which are missing or incomplete for some subpopulations (especially for PANS).

3. Results

3.1 Descriptive Statistics

3.1.1 Psychometric Data

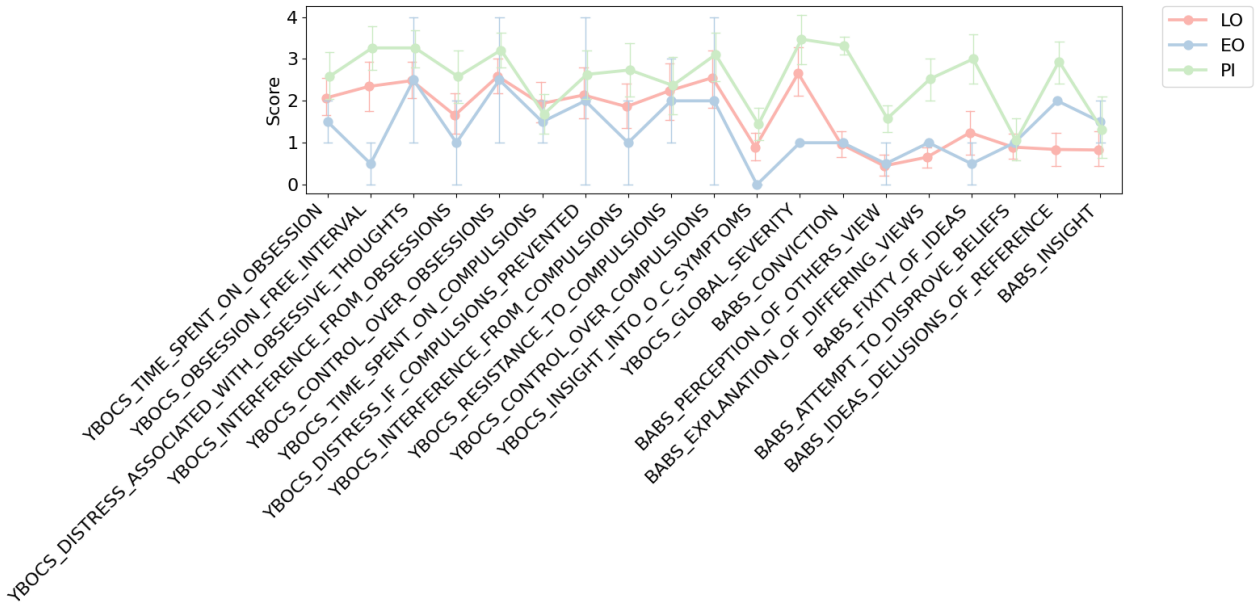

Figure 2. Plot line describing mean scores and standard errors for each YBOCS and BABS subcomponent divided based on the diagnostic subtype.

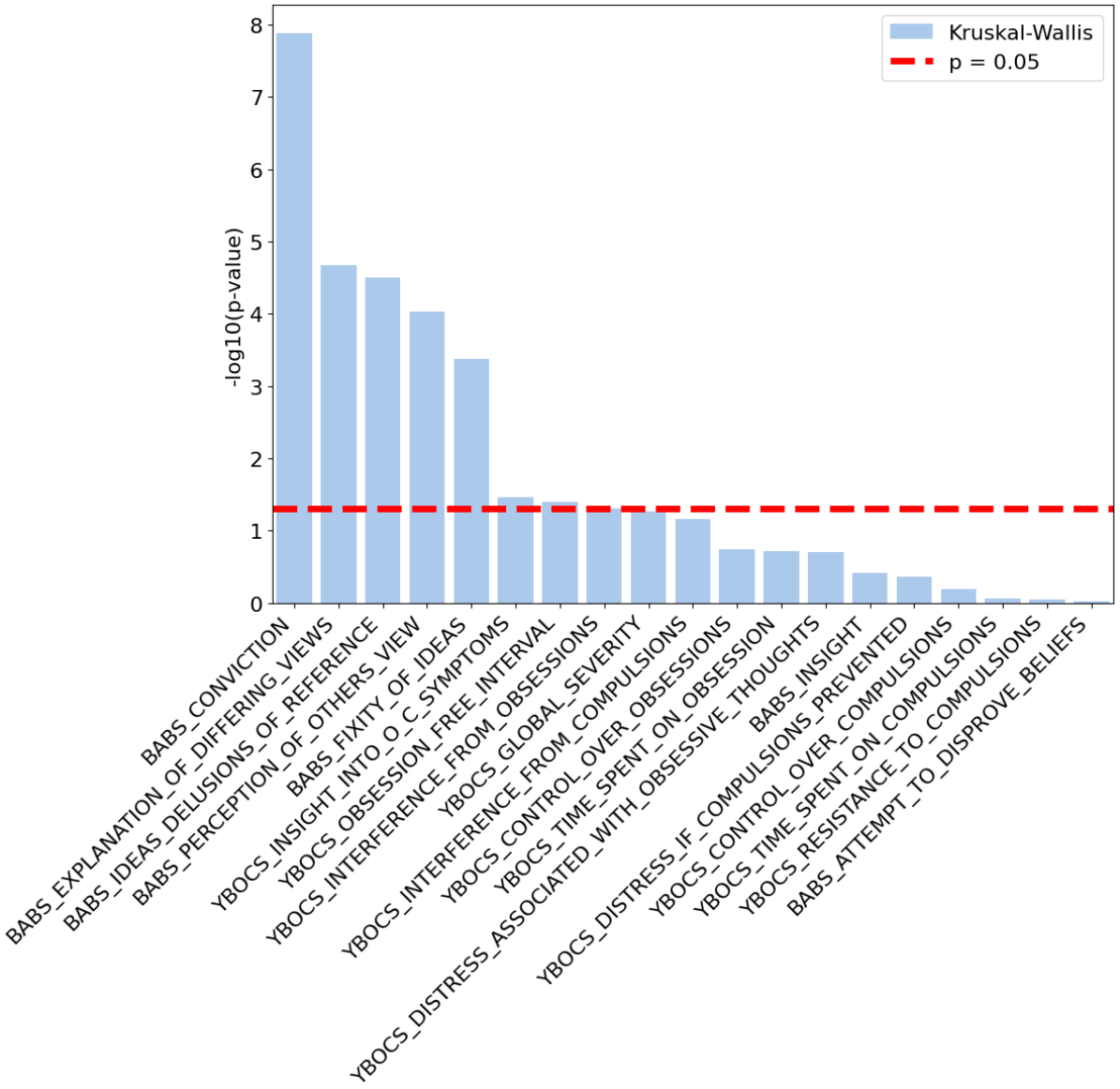

Figure 3. Bar plot for the log10 p-values Kruskal-Wallis test of each BABS and YBOCS component between diagnostic subgroups. The red dashed line marks the threshold for statistical significance.

A nonparametric statistical analysis (Kruskal–Wallis, as the data distribution did not meet normality criteria – Figure 3) was conducted to compare diagnostic groups (EO, LO, PI) across all clinical variables considered. Results showed significant differences among groups for several BABS subscales, particularly for Conviction ($p = 1.3\times10^{-8}$), Fixity of Ideas ($p = 4.2\times10^{-4}$), Ideas/Delusions of Reference ($p = 3.1\times10^{-5}$), and Explanation of Differing Views ($p = 2.1\times10^{-5}$).

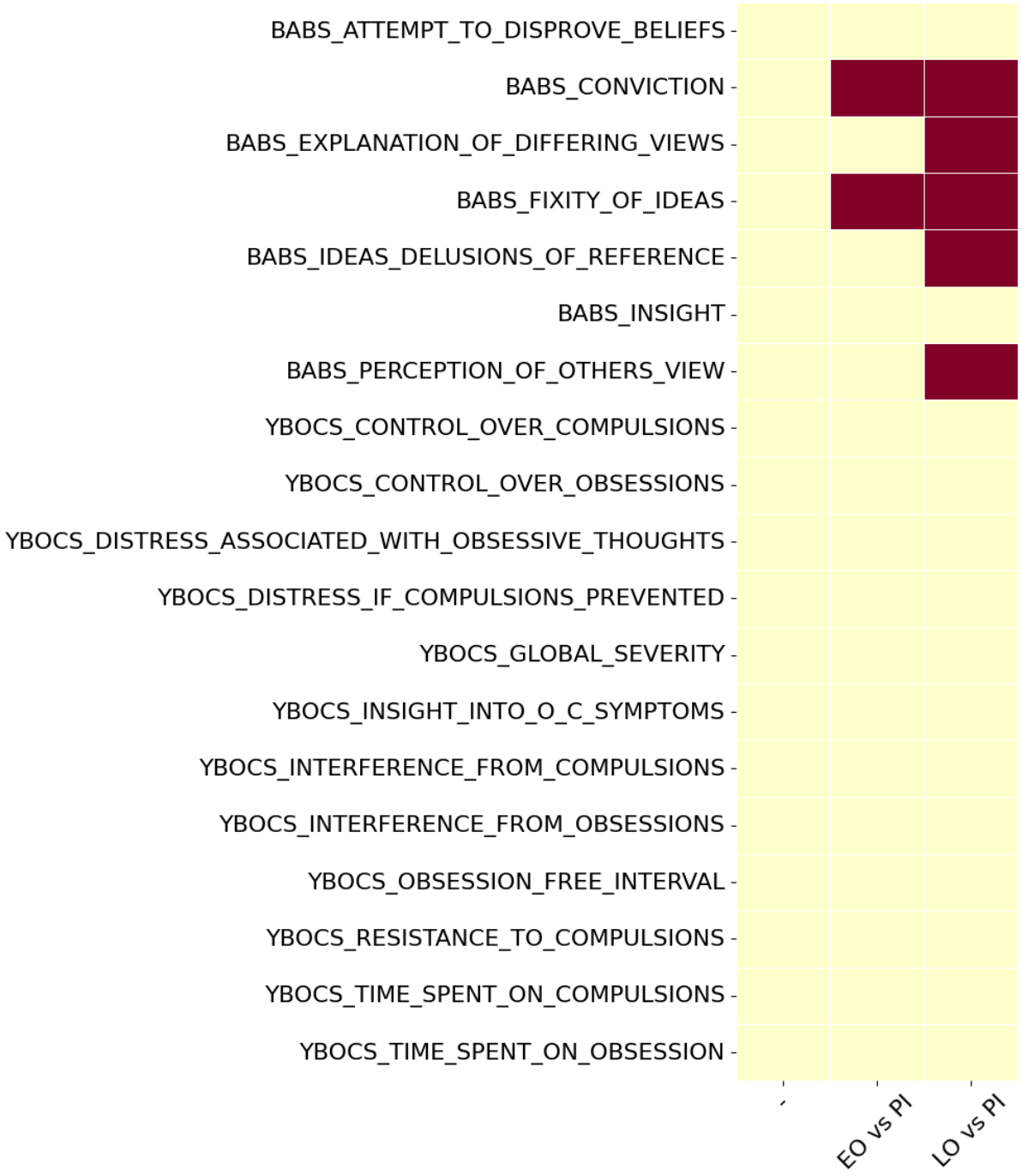

Figure 4. Heatmap for pairwise group comparison between OCD subgroups based on the YBOCS and BABS item scores.

Figure 4 describe pairwise comparisons between OCD subgroups (i.e., OCD PI vs EO, The two columns correspond to EO vs PI and LO vs PI comparisons – the dark red cells indicate statistically significant differences between groups, light yellow cells non-significant results. Not surprisingly, the most significant result is for BABS items and PI vs the remaining categories. No significant differences emerged between YBOCS severity and the defined categories.

3.1.2 Neurocognitive Data

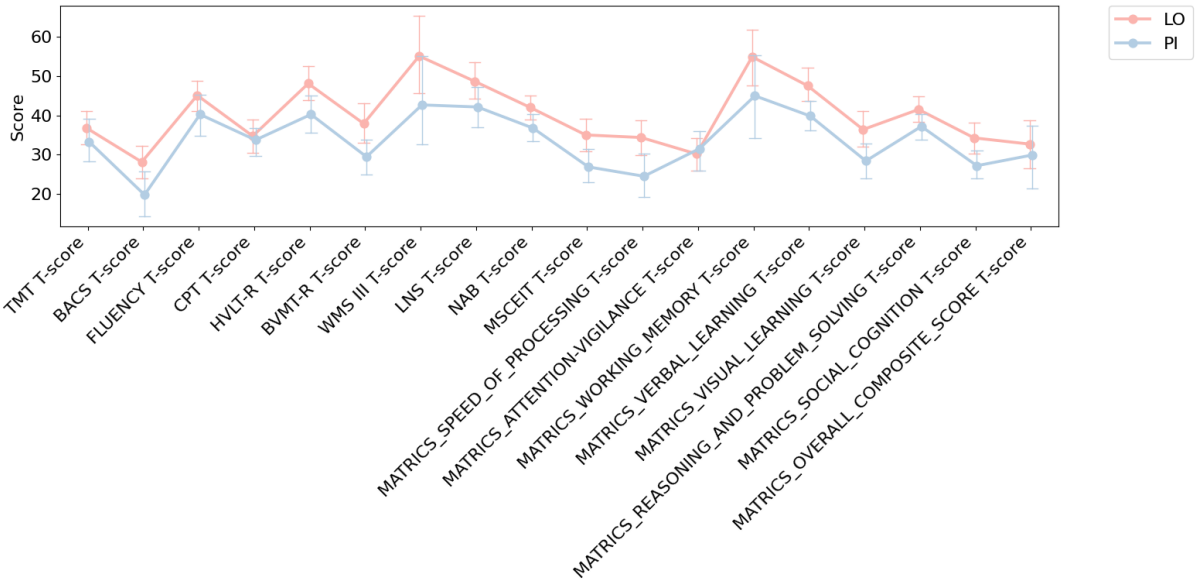

Figure 5. Line plot describing mean T-scores and standard errors for the different cognitive measures as defined across the two groups PI and LO. No Neurocognitive data were available for the remaining subgroups.

As Figure 5 shows, there is a tendency for higher cognitive performance in the LO subgroup, as defined by the applied neurocognitive battery, across the board compared with the PI subgroup. The largest gaps appear to be observed for speed processing MSCEIT, BACS and HVLT-R where PI subjects appear to score on average 5-10 T scores lower.

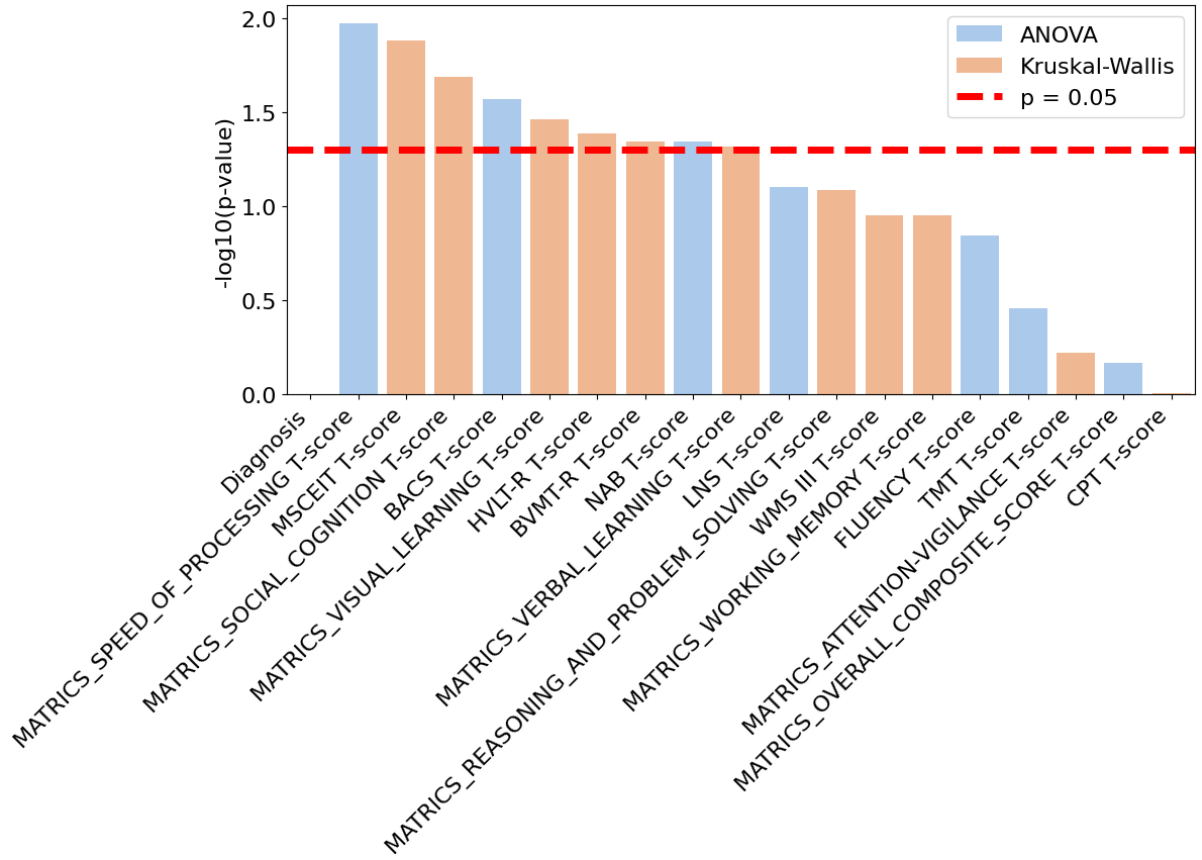

Figure 6. Bar plot describing the log-10(p-values) for each MATRICS-defined neuropsychological test derived from ANOVA (blue bars) and Kruskal-Wallis tests (orange bars).

As shown in Figure 6, the tests exceeding the significance threshold (red-dashed line) are the MATRICS speed of processing, MSCEIT, BACS, HVLT-R, and BVMT-R T-scores, largely in line with expectations related to the .

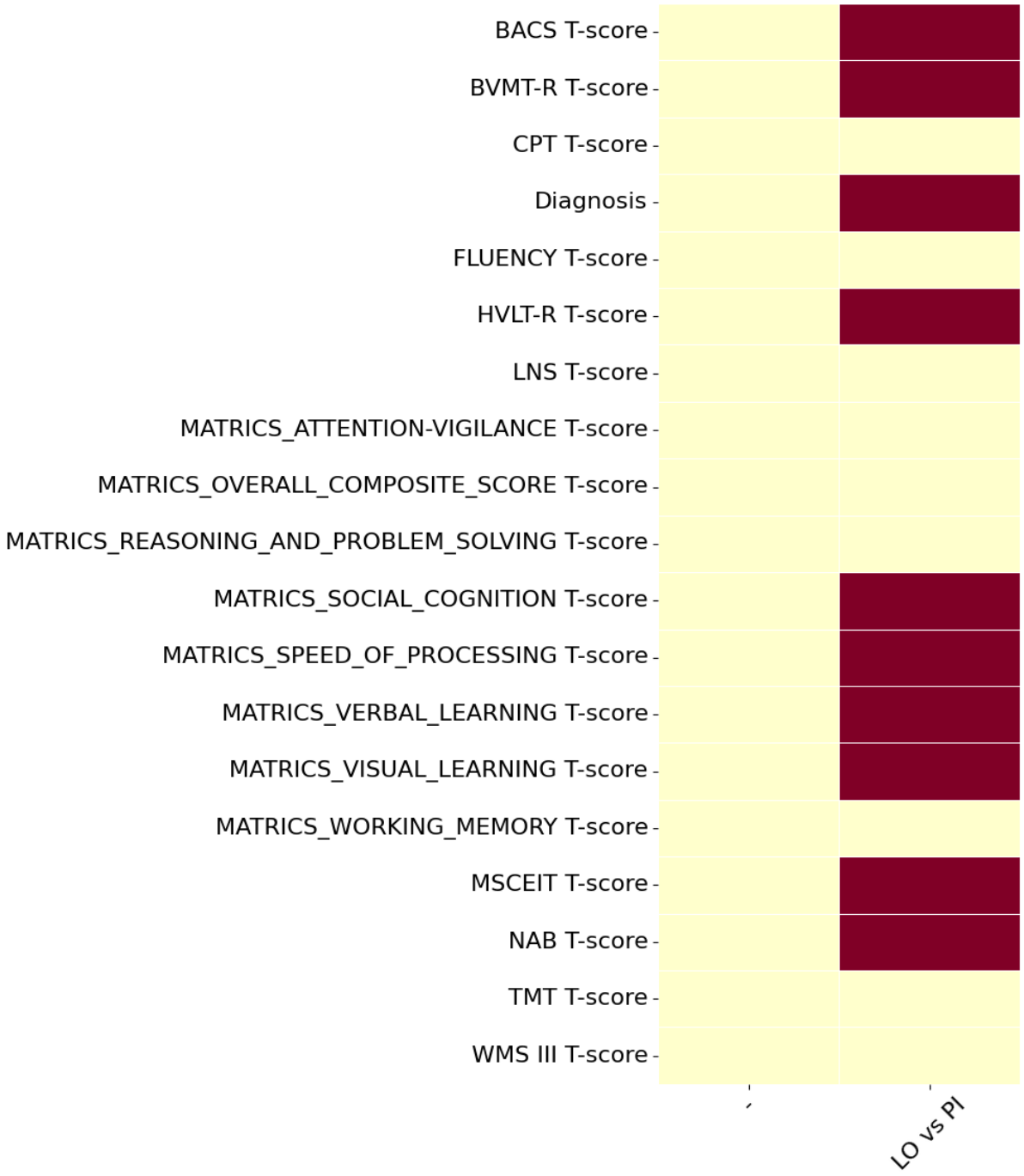

Figure 7. Heatmap describing pairwise comparisons of MATRICS subtasks T-scores divided based on LO vs PI subgroups.

As described in figure 7 and in line with the results, PI subjects performed significantly worse in verbal learning (HVTL-R), visual learning (BVMT-R), Fluency, Reasoning and Problem Solving, Social Cognition (MSCEIT).

3.1.3 Polysomnography

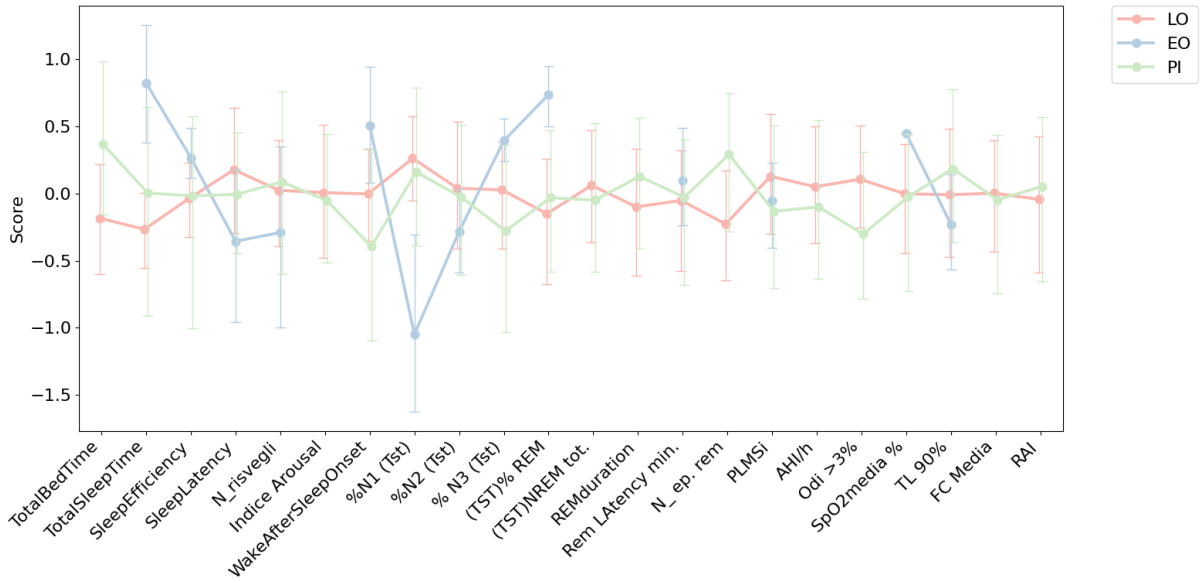

Figure 8. Line plot for the z-normalized polysomnographic variables across the three different subgroups for which data was available.

Figure 8 describes the pattern of several different polysomnographic variables for the different study subgroups. With few notable exceptions, there is a relatively overlap for the z-standardized sleep patterns. EO data are to be interpreted with cautions as they relate to merely two individuals and therefore the comparison with this group should be considered unreliable. Overall, PI subjects tend to display a flatter profile with reduction in %REM and total sleep time, whilst LO appear to show greater stability across most indices.

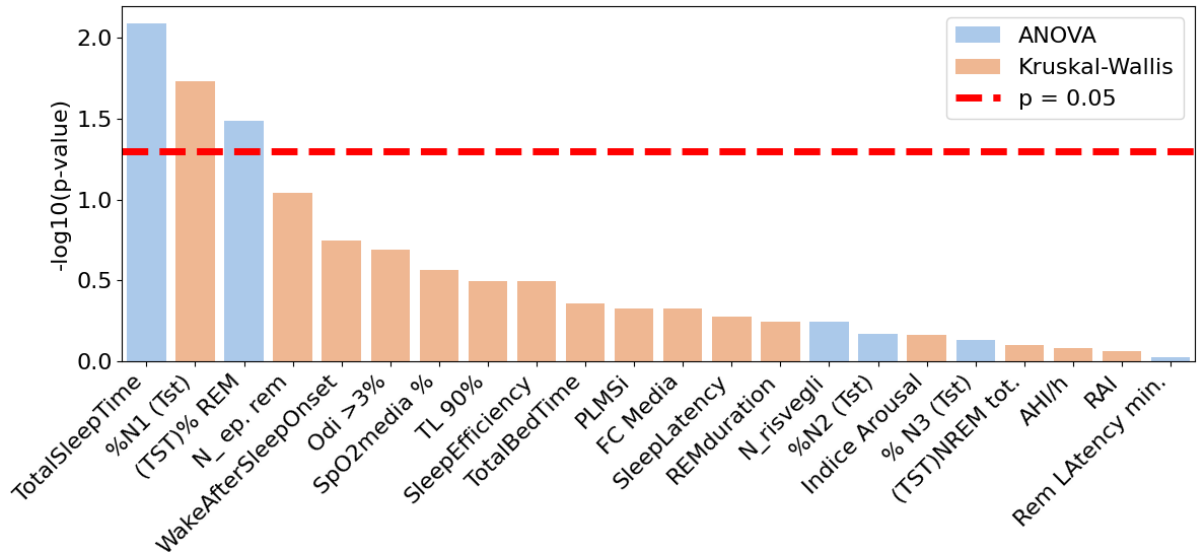

Figure 9. Bar plot for ANOVA and Kruskal-Wallis for -log10(p-value) for intergroup sleep comparisons.

As was the case for the preceding analyses, figure 9 display a bar chart for the -log10(p-value) for ANOVA and Kruskal-Wallis of the comparisons in the polysomnographic variables in the different study groups. Total Sleep time, %N1 and %REM cross the threshold for significance (red dashed line p=0.05).

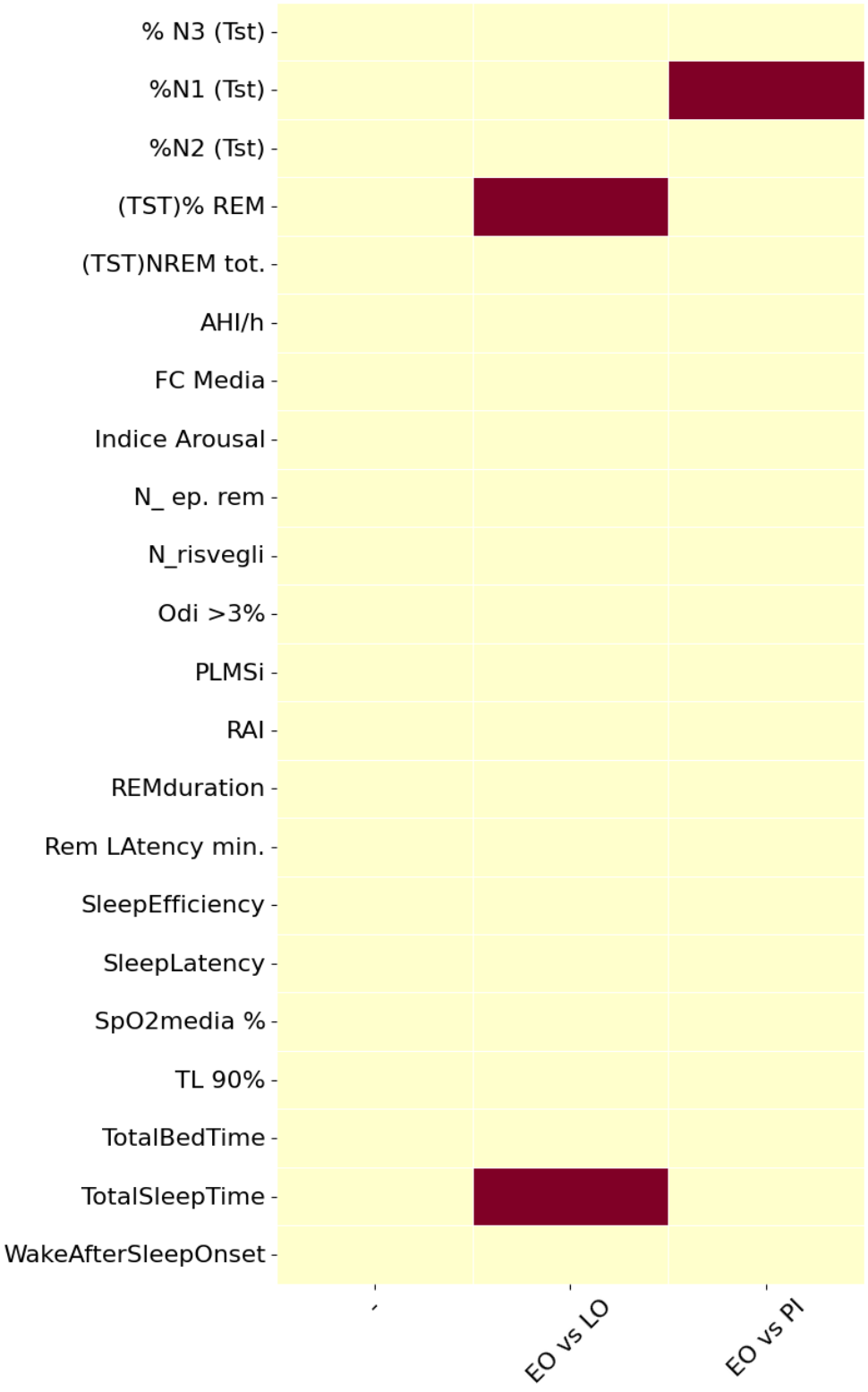

Figure 10. Heatmap for pairwise sleep differences among study groups.

In our sample we found evidence for significant differences in %N1 and decreased REM proportion among EO (Figure 10). LO and PI present fewer differences, with the notable exception of lower total sleep time and % REM.

For the EO subgroup only 2 subjects had the polysomnographic tests available, so this element could not be included in the analysis

Due to the limited availability of data for the EO group, isolated observations (single values) were not included in the graphical displays to avoid misleading interpretations stemming from insufficient sample sizes.

3.1.4 Biomarkers

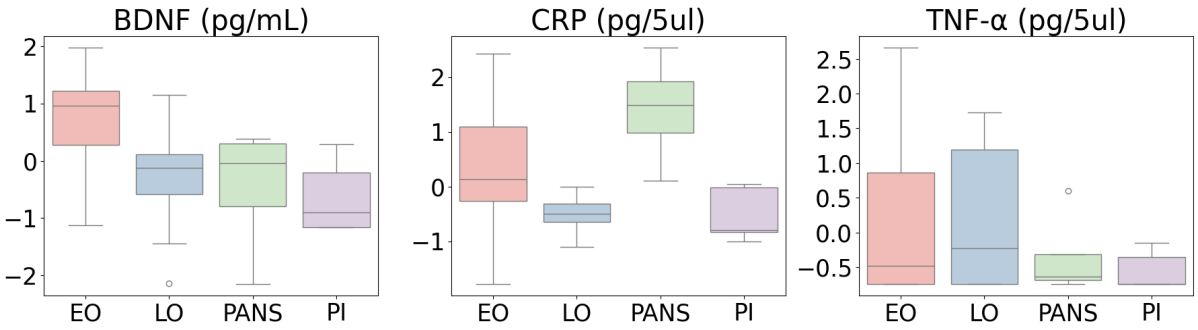

Figure 11. Peripheral blood biomarkers for BDNF, CRP and TNF-alfa across study subgroups

Figure 11 proposes a panel describing the box and whiskers plots for the three selected peripheral biomarkers from left to right: BDNF, CRP and TNF-alfa. BDNF appear highest in EO with relatively similar levels for LO, PANS and PI.

Shapiro–Wilk Tests for the selected biomarkers across study groups. Overall, the distribution follow a normal distribution with the exception of TNF-alfa.

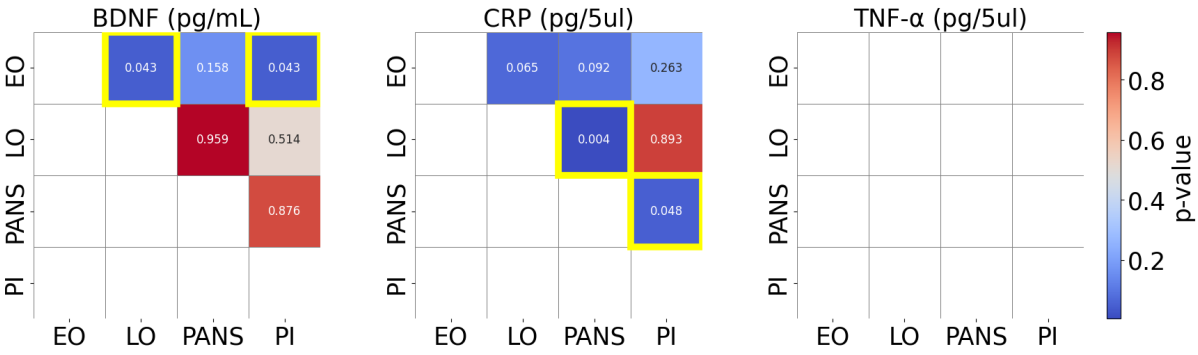

Figure 12. Heatmap of pairwise Kruskal-Wallis post-hoc comparisons.

As figure 12 shows, we found evidence for possible differences in BDNF levels among study groups with significantly higher level of unadjusted BDNF in EO as compared with LO or PI (p=0.043) and lower CRP in PANS as compared with both LO (p=0.004) and PI (p=0.048).

Biomarker	Subgroup	N total	N missing	% valid	% missing
BDNF (pg/mL)	Early Onset	24	10	58.33%	41.67%
	PANS	29	15	48.28%	51.72%
	Late Onset	36	32	11.11%	88.89%
	Poor Insight	19	14	26.32%	73.68%
CRP (pg/5µl)	Early Onset	24	10	58.33%	41.67%
	PANS	29	15	48.28%	51.72%
	Late Onset	36	32	11.11%	88.89%
	Poor Insight	19	14	26.32%	73.68%
TNF-α (pg/5µl)	Early Onset	24	10	58.33%	41.67%
	PANS	29	15	48.28%	51.72%
	Late Onset	36	32	11.11%	88.89%
	Poor Insight	19	14	26.32%	73.68%

Table 1. Description for missing items for each studied translational biomarker.

3.3 Principal Component Analysis Results

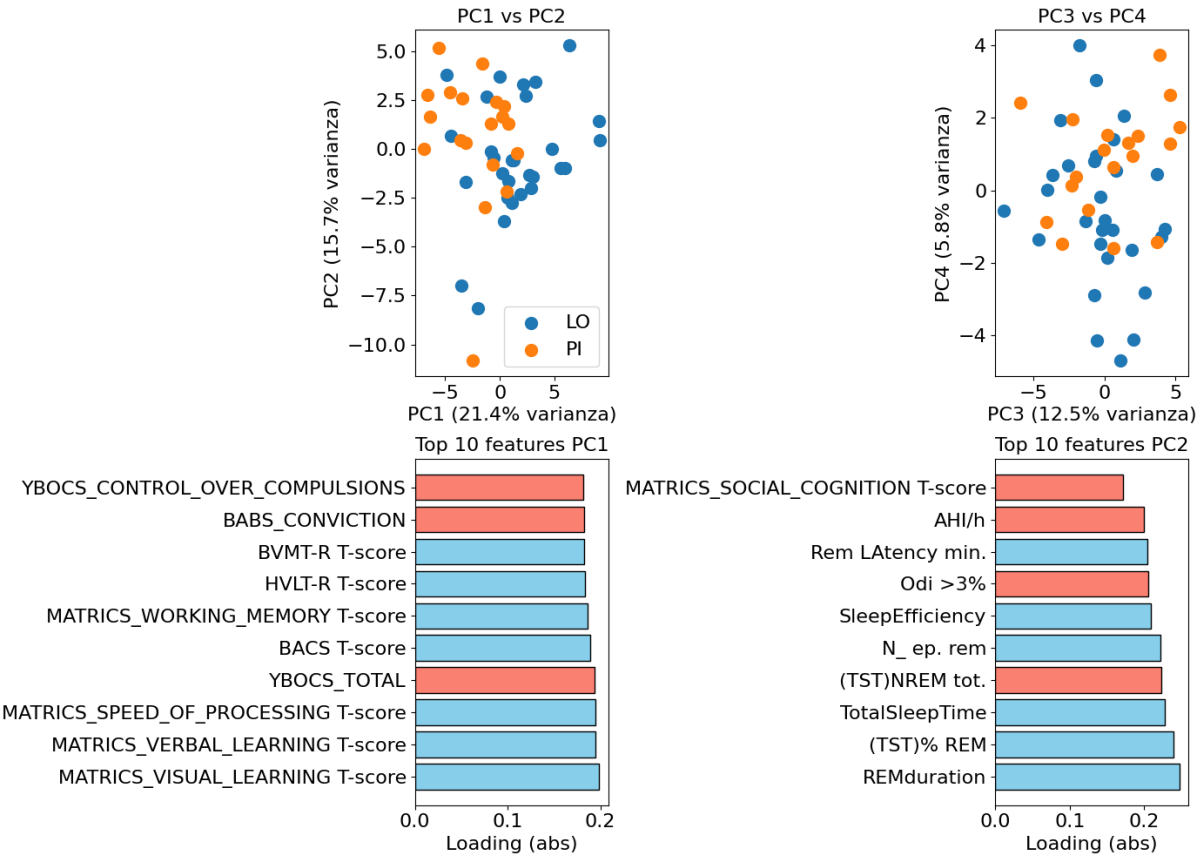

Figure 13. Scatterplot for the Principal Component Analysis of clinical, cognitive and polysomnographic variables.

PCA is useful for capturing significant latent structures within clinical data, enabling a concise visualization of differences among diagnostic groups. In particular, PCA was conducted to reduce the dimensionality of the variable set and to identify latent covariation patterns among clinical measures. The figure shows the distribution of participants along the first four principal components (PC1–PC4).

Top panel shows scatterplots describing participants divided based on the four principal component and color coded by the selected OCD subtypes (orange PI and LO blue). Bottom panel show the top 10 variable loading contributing to each principal component and resulting in

- PC1 (21.4% variance) and driven mainly by YBOCS control over compulsion and BABS-convinction subitem along with T-scores for MATRICS-defined Working memory, verbal and visual learning and speed of processing.
- PCS2 (accounting for 15.7 variance) is accounted by MATRICS-Social Cognition, Sleep

Efficiency, REM-related metrics (duration, latency, % REM) and respiratory indices (AHI, ODI).

Summarizing, the first two components explain the largest share of total variance (PC1: 21.4%, PC2: 15.7%) and allow a partial separation between diagnostic subgroups (LO vs PI), suggesting multivariate differences in psychometric and neurocognitive profiles.

3.4 Classification Model Results

3.4.1 Unsupervised Models

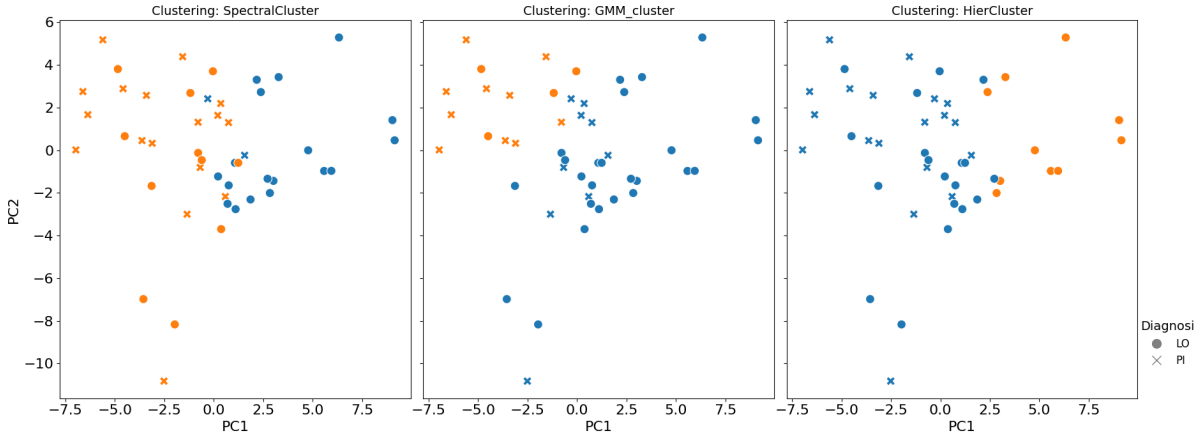

Figure 14. Scatterplot illustrating different unsupervised clustering algorithm, Spectral Clustering, Gaussian Mixture Model (GMM) and Hierachical clustering applied to the same PCA-reduced dataset.

Figure 14 describe three scatterplot for three different unsupervised clustering algorithms. Across different methods, there is evidence for partial overlapping between LO and PI and no clear line separating the two. This observation may be in line with a dimensional framework rather than categorical in defining OCD phenotypes.

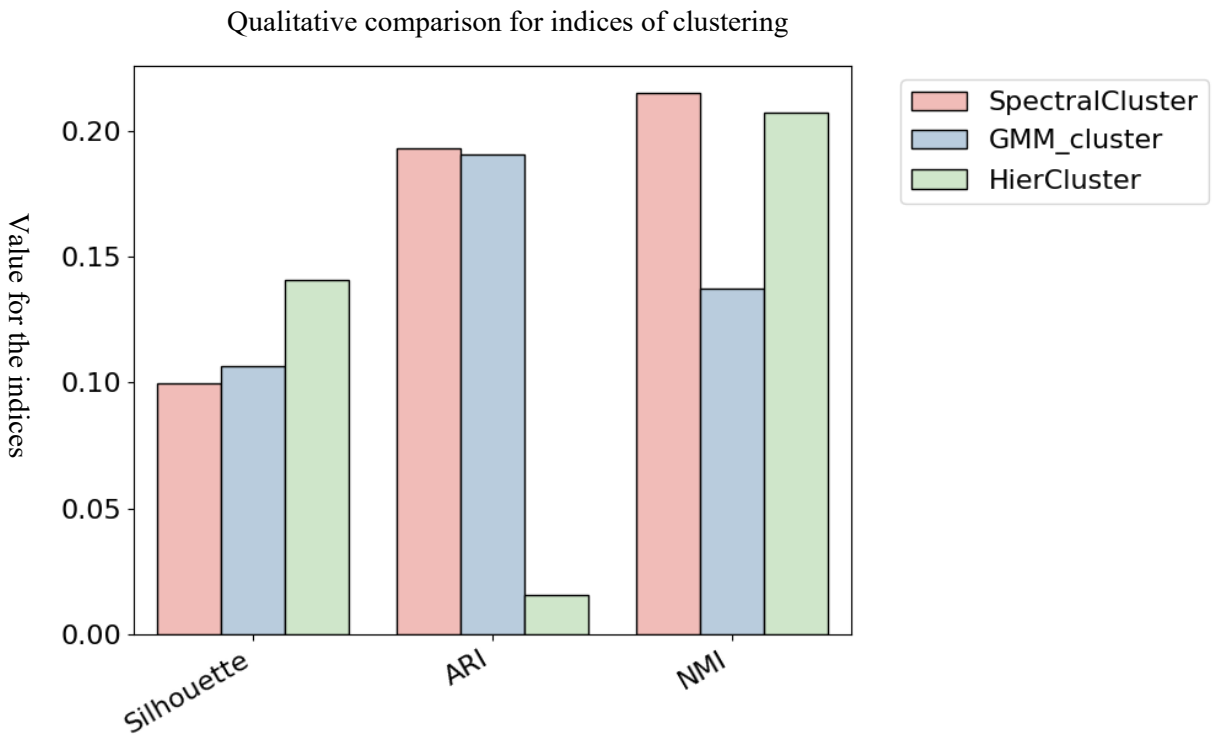

Figure 15. Bar plot describing three quantitative indices of clustering performances across the three different applied methods.

To evaluate the presence of latent subgroups within the sample, three unsupervised clustering algorithms were applied to the standardized data: Spectral Clustering, Gaussian Mixture Model (GMM), and Hierarchical Clustering. These methods were chosen because they allow specification of the number of clusters to identify.

Spectral Clustering leverages eigen-decomposition of the similarity graph among subjects, projecting data into a spectral space in which clusters are more easily separable via partitioning methods (e.g., k-means).

GMM assumes that data arise from a mixture of latent Gaussian distributions and estimates each component's parameters using the Expectation–Maximization (EM) algorithm, assigning subjects a probability of belonging to each cluster rather than a hard classification.

Hierarchical Clustering builds a hierarchy of groupings based on distances among observations using an agglomerative (bottom-up) approach, progressively merging clusters into a tree structure (dendrogram).

To assess clustering quality, multiple metrics were computed. We used unsupervised metrics that evaluate internal cohesion and separation without diagnostic labels:

Silhouette Score (higher values indicate greater internal consistency).

Because diagnostic labels were available, supervised metrics were also computed to assess correspondence between obtained clusters and clinical classes:

Adjusted Rand Index (ARI), measuring agreement between predicted and true partitions while correcting for chance;

Normalized Mutual Information (NMI), quantifying shared information between predicted and true classifications, normalized by entropy.

All metrics were calculated for each clustering method and compared using a grouped bar chart, enabling a comparative evaluation of the discriminative power of the different approaches.
All algorithms tend to show low silhouettes values (<0.15), therefore, confirming weak internal cohesion and considerable overlap among clusters.

3.4.2 Supervised Models

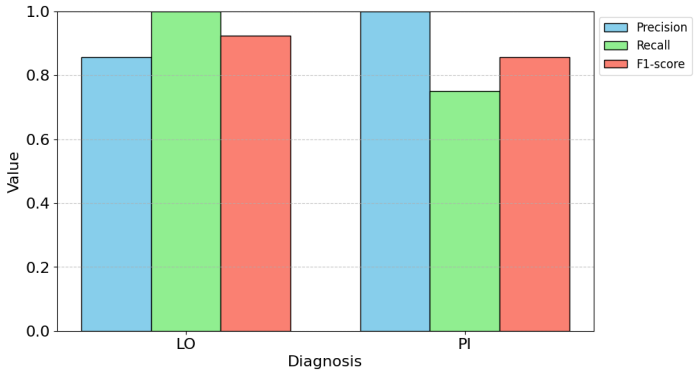

Figure 16. Bar plot describing precision, recall and F1-score for each group (LO and PI). Precision represents the proportion of correctly classified predicted classes. Recall the proportion of actual cases correctly identified by the model. F1-score harmonic mean of precision and recall, reflecting a balanced performance.

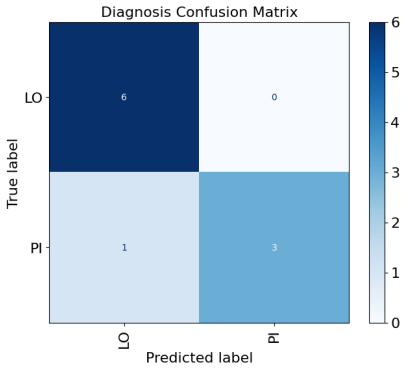

Figure 17. Confusion matrix displaying model predictions (columns) versus true labels (rows). Diagonal cells represent correctly classified subjects, while off-diagonal cells represent missclassifications.

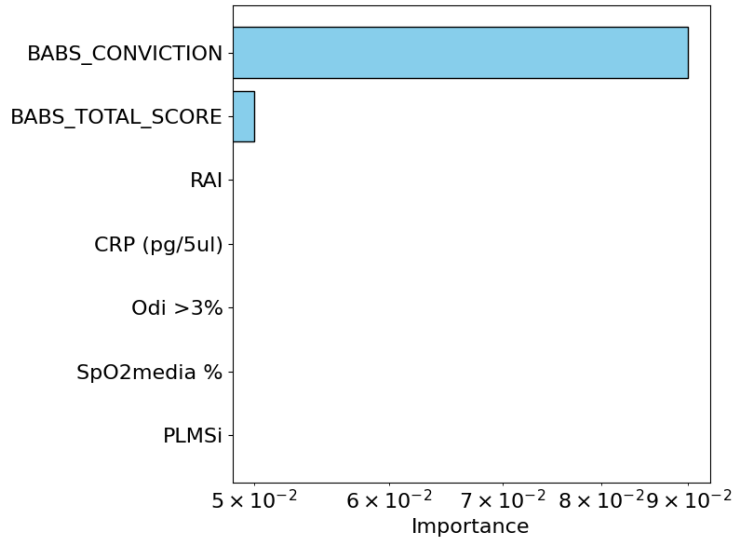

Figure 18. Horizontal bar plot describing the relative importance of predictor variables contributing to the classification model.

To assess the discriminative ability of the variables in distinguishing LO vs PI, we used a Random

Forest Classifier, which allows class imbalance to be handled by assigning balanced class weights.

The dataset was split into training (80%) and test (20%) sets.
Model performance was evaluated—for each group—via precision, recall, and F1-score. In the corresponding bar chart, each metric is shown for both diagnoses, allowing a visual comparison of performance across categories.

High precision values indicate a low incidence of false positives, whereas high recall denotes good ability to correctly identify subjects belonging to a given class. F1-score is the harmonic mean of precision and recall and thus summarizes the overall balance between the classifier's sensitivity and specificity.

The confusion matrix shows the distribution of correct and incorrect predictions for each diagnostic group. A predominance of values along the main diagonal indicates good model ability to correctly discriminate between the two diagnostic categories.

Finally, feature importance, obtained by evaluating the degradation in classifier performance when removing features one by one, highlights the variables that contribute most to discriminating LO from PI. Features with the highest importance values represent clinical or neurocognitive factors that most strongly influence classification, offering potential key indicators for characterizing disorder subtypes. Overall, the classifier achieved high overall accuracy with a precision of 0.85-1.0, a recall of 0.75-1.0 and an F1 of 0.9. Therefore, despite a relatively weak separability achieved with the unsupervised model, the supervised model appears to present a more robust discriminative signal between the studied subgroups. BABS conviction in this framework appears to be the most significant predictor, far exceeding all others in contribution magnitude, with BABS total score, RAI (arousal index), CRP, oxygen saturation and PLMS representing further significant predictors.

3.5 Regression model for cognitive performances, psychometric testing and translational

biomarker candidates

Variable	Overall (n = 50)	p-value	Test	OCD Early Onset (n = 2)	OCD Late Onset (n = 29)	OCD Partial Insight (n = 19)
Age (years)	44 [32–56]	0.619	Kruskal–Wallis	37.5 [27.8–47.2]	43 [32–51]	46 [35–62]
Height (cm)	75 [60–84]	0.770	Kruskal–Wallis	82 [82–82]	70 [60.5–84]	75 [59–81.5]
Weight (kg)	170 [160–175]	0.317	Kruskal–Wallis	182 [182–182]	170 [160–174.8]	168.5 [163.5–175]
Father's age at birth	33 [30–40]	0.306	Kruskal–Wallis	—	32.5 [29.2–37.8]	33 [31–43]
Mother's age at birth	27 [25–35]	0.555	Kruskal–Wallis	—	28.5 [23.8–32.8]	27 [25–35]
Y-BOCS total	25 [18–31.5]	0.338	Kruskal–Wallis	16.5 [10.8–22.2]	24 [10–32]	26 [21–31]
BABS total score	8 [4–12]	**<0.001**	Kruskal–Wallis	5.5 [4.8–6.2]	6 [0–8]	**13 [11.5–14.5]**
Sex – Male	31 (62.0 %)	0.506	Chi-square	2 (100.0 %)	18 (62.1 %)	11 (57.9 %)
Sex – Female	19 (38.0 %)			0 (0.0 %)	11 (37.9 %)	8 (42.1 %)

Variable	Overall (n = 50)	p-value	Test	OCD Early Onset (n = 2)	OCD Late Onset (n = 29)	OCD Partial Insight (n = 19)
Psychiatric comorbidities – Yes	33 (66.0 %)	0.527	Chi-square	2 (100 %)	18 (62.1 %)	13 (68.4 %)
Psychiatric comorbidities – No	17 (34.0 %)			0 (0 %)	11 (37.9 %)	6 (31.6 %)
Socio-economic status – Low	24 (48.0 %)	0.854	Chi-square	1 (50.0 %)	15 (51.7 %)	8 (42.1 %)
Socio-economic status – Average	22 (44.0 %)			1 (50.0 %)	11 (37.9 %)	10 (52.6 %)
Socio-economic status – High	4 (8.0 %)			0 (0 %)	3 (10.3 %)	1 (5.3 %)
Education – Middle school	28 (56.0 %)	0.901	Chi-square	1 (50.0 %)	15 (51.7 %)	12 (63.2 %)
Education – High school	18 (36.0 %)			1 (50.0 %)	11 (37.9 %)	6 (31.6 %)
Education – University	4 (8.0 %)			0 (0 %)	3 (10.3 %)	1 (5.3 %)
Family history of mental disorder – Yes	20 (40.0 %)	0.629	Chi-square	1 (50 %)	13 (44.8 %)	6 (31.6 %)
Family history of bipolar disorder – Yes	47 (94.0 %)	0.562	Chi-square	2 (100 %)	28 (96.6 %)	17 (89.5 %)
Family history of major depression – Yes	35 (70.0 %)	0.501	Chi-square	1 (50 %)	19 (65.5 %)	15 (78.9 %)
Family history of schizophrenia – Yes	47 (94.0 %)	0.074	Chi-square	2 (100 %)	29 (100 %)	16 (84.2 %)

Variable	Overall (n = 50)	p-value	Test	OCD Early Onset (n = 2)	OCD Late Onset (n = 29)	OCD Partial Insight (n = 19)
Family history of suicide (completed/attempted) – Yes	42 (84.0 %)	0.404	Chi-square	2 (100 %)	23 (79.3 %)	17 (89.5 %)
Any psychotropic therapy – Yes	36 (72.0 %)	0.061	Chi-square	0 (0 %)	21 (72.4 %)	15 (78.9 %)

Table 2. Main sociodemographic and clinical features for the subsample included in the linear regression model. For two individuals, the family history of suicide attempts was missing.

Table 2 describes the main features of the subsample included in the linear regression model. No significant differences emerge based on the OCD subgroup, with the expected exception of BABS severity for the poor insight subgroup, which presents a higher level. For this analysis the sample comprised 50 adults (median age = 44 years old) with 38 % of the sample female as sex assigned at birth and with 44 % holding a high-school diploma or higher. Median total Y-BOCS score was 25, indicating moderate to severe symptom severity but with no significant differences across subgroups. Overall, polysomnographic data were available for 41 subjects across the four subgroups; therefore, for this sub-analysis, we focused only on peripheral blood biomarkers and clinical variables. Median BABS total score was 8, which, not surprisingly, was significantly higher in the PI subgroup as compared with the remaining sample (Table 1).

Correlation Between Neurocognitive and Psychometric Tests in LO vs PI

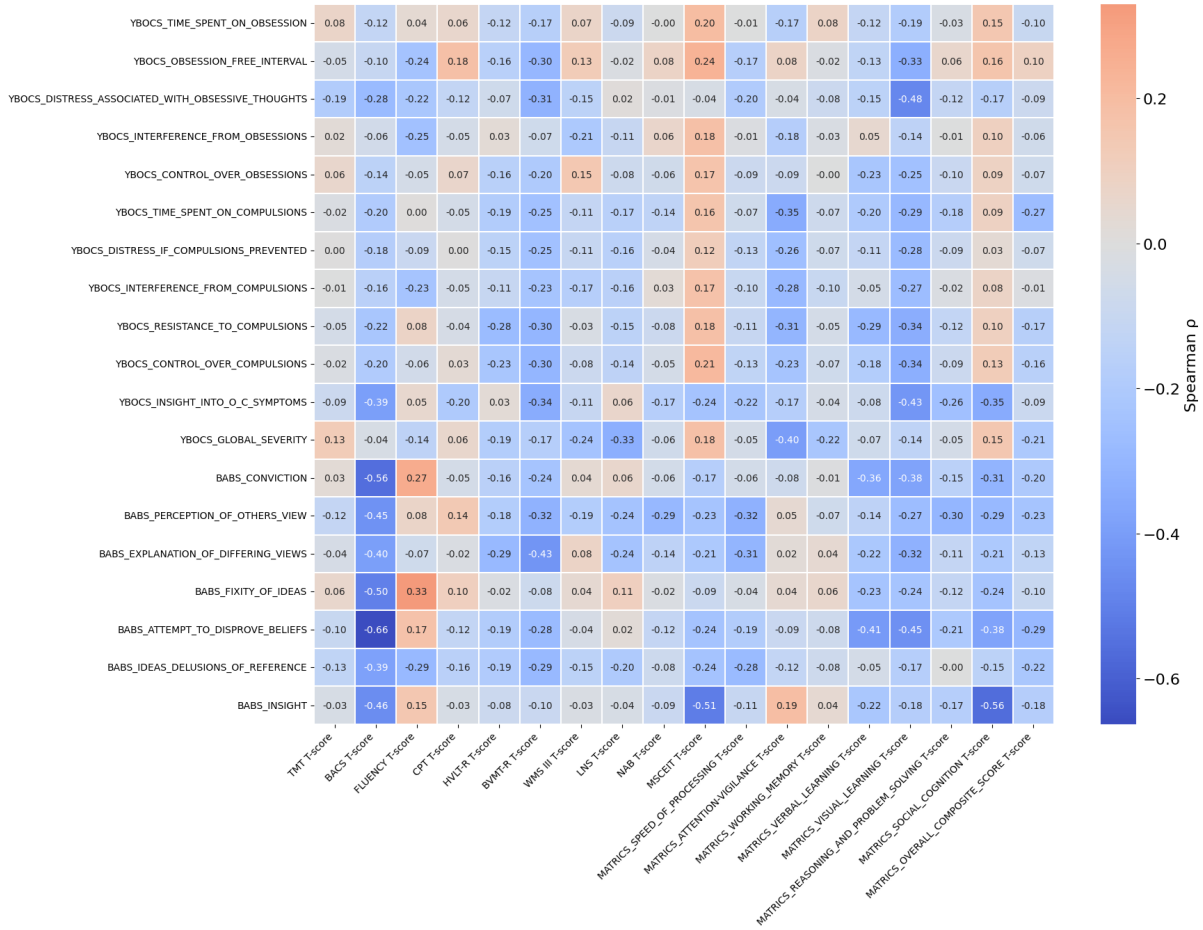

Figure 19. Heatmap for the Spearman's rank correlation between Yale Brown Obsessive Compulsive Scale (YBOCS), Brown Assessment of Belief Scale (BABS) and cognitive functions (MATRICS) for LO subjects.

As described in figure 19, overall we found a negative correlation among LO subgroup subjects between both BABS and YBOCS total score and cognitive performances defined according to T-scores for MATRICS subtasks with the most notable for social cognition and BABS-defined insight.

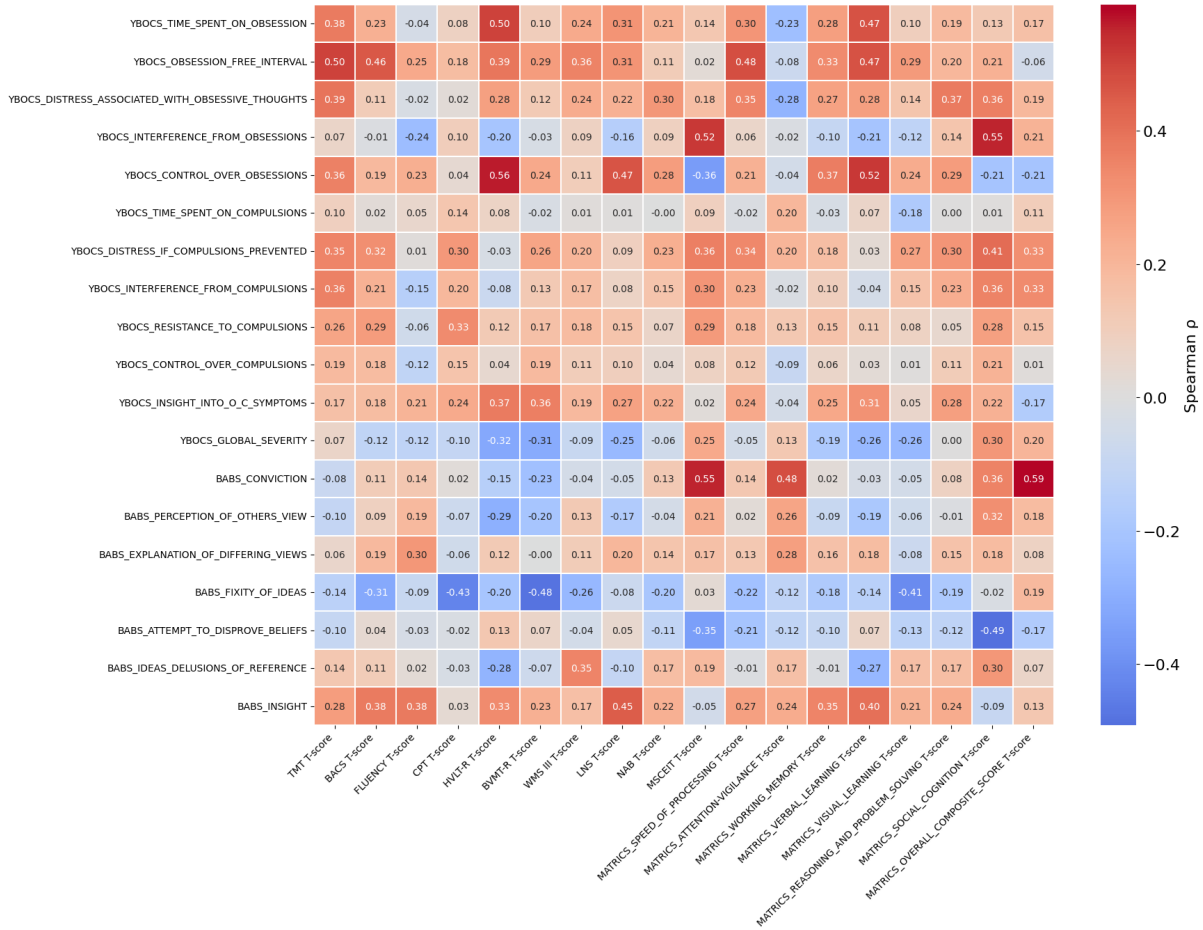

Figure 20. Heatmap describing the Spearman rank correlation for YBOCS total and each subcomponent, BABS total score and each subcomponent along with all MATRICS-defined subtasks among PI subjects.

Figure 20 describe the same type of correlation between psychopathology (i.e., BABS and YBOCS scores) and cognitive performances (i.e., MATRICS subtasks), suggesting that among PI there might be a correlation in the opposite direction as compared to LO. More specifically, we observe a tendency for a direct association for social cognition (MSCEIT T-scores) and BABS conviction or for BABS conviction and MATRICS Overall composite T-score.

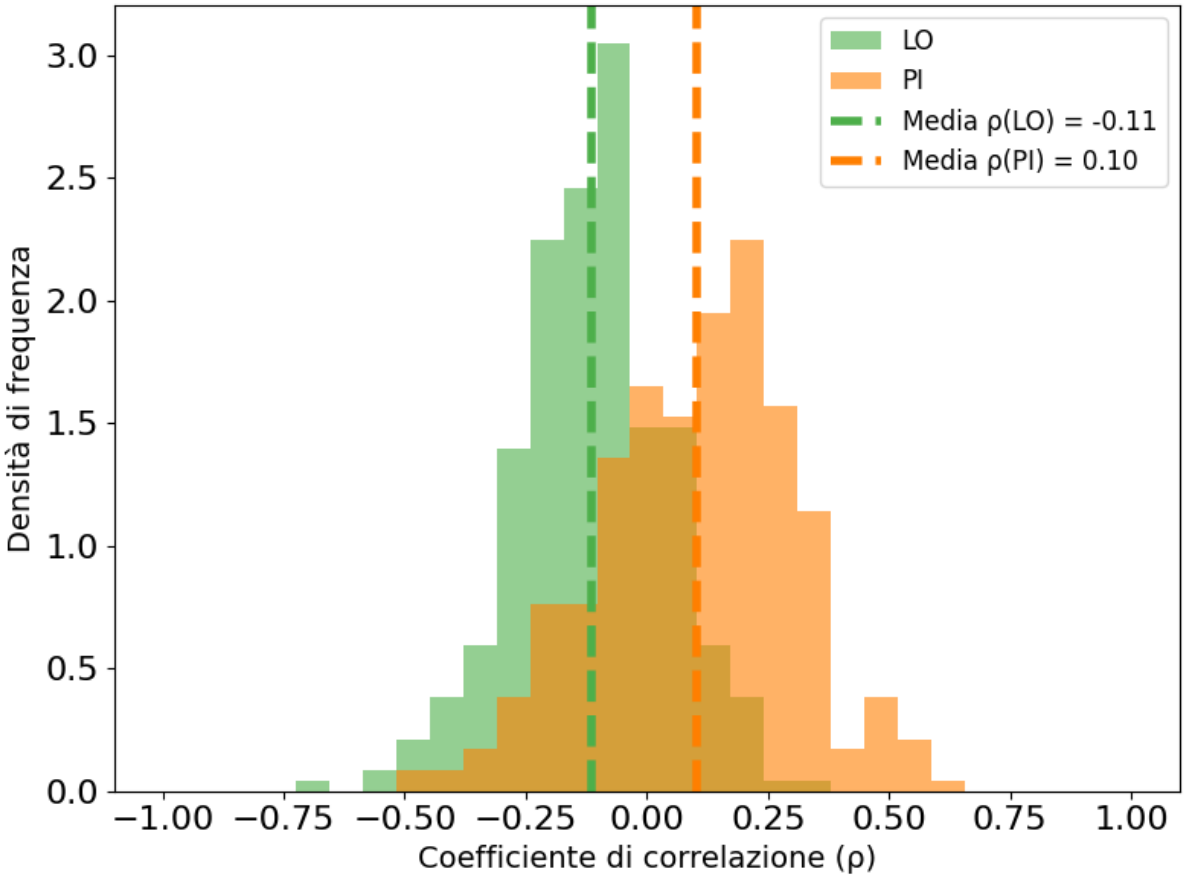

Figure 21. Histogram describing the distribution of Spearman coefficient between cognitive and clinical variables in LO and PI (green and orange, respectively)

Figure 21 describes the distribution of the Spearman coefficient between clinical variables and cognitive performances. Values were log-normalised and standardised (z-scores) before computing correlations. In the LO, there is a weak negative or null association between clinical and cognitive indices. On the other hand, among PI subjects, there is a right-shifted distribution suggesting a weak positive association.

With the intent of further exploring the potential association of cognitive functions, clinical severity and the tested biomarkers in peripheral blood, we used a regression model with MATRICS-defined t scores and percentiles as the dependent variable, alternatively substituted and corrected for age and education level. Demographic variables were recoded as follows:

- *education* dichotomized at ≥ 2 = higher education (educ_high = 1);
- *age* treated as continuous;
- medication variables (antidepressant, mood stabilizer, antipsychotic, benzodiazepine) as binary covariates.

Outcome and predictor definition (table 3)

- **Outcomes:** All MCCB T-scores and percentiles for the seven domains.
- **Predictors:** Clinical scales (BABS total and subitems; Y-BOCS total and subscales) and biomarkers (BDNF_z, TNF-α_z, CRP_z).
- **Covariates:** Age, education, and in augmented models, PSQI and medication classes.

Model structure

Two hierarchical linear regression models were fit for each *outcome* × *predictor* pair:

Model	Formula (conceptual)	Purpose
Simplified	MATRICS_domain ~ clinical_predictor + age + educ_high + biomarkers_z	Test direct clinical–cognitive association adjusting for demographics and biomarkers
Augmented	MATRICS_domain ~ clinical_predictor + age + educ_high + biomarkers_z + psqi + antidepressant + mood_stabilizer + antipsychotic + benzodiazepine	Evaluate added explanatory value of sleep and medication covariates

Table 3. Description for the main regression models applied.

For both models, diagnostic metrics included adjusted R^2, Akaike Information Criterion (AIC), and leave-one-out cross-validation root mean square error (LOOCV RMSE).

2.6.4 Multiple testing correction

For each cognitive outcome, Holm and Benjamini–Hochberg (BH) corrections were applied separately within outcome × model families for (a) clinical and (b) biomarker terms. Only Holm-corrected results at $p < 0.05$ were considered significant.

2.6.5 Visualization

Standardized regression coefficients (β) were plotted in heatmaps (ggplot2) showing the direction and magnitude of associations between each MATRICS domain and clinical predictors, controlling for age and education. Warmer colors (red) indicate negative relationships, cooler (green) positive. Significance after Holm correction was indicated by asterisks (*p < 0.05; **p < 0.01; **p < 0.001).

Although both the simplified and augmented models were implemented, model diagnostics indicated that the augmented specification (including PSQI and psychotropic medications) yielded negligible improvement in adjusted R^2 and RMSE, with $\Delta AIC < 0$ in only 8 % of models. Therefore, the simplified model was retained as the primary analytic framework for interpretation due to superior parsimony and stability.

MATRICS Domain	Clinical Predictor	β (± SE)	t	p adj (Holm)	Direction	Interpretation
Social Cognition (T-score)	BABS Total Score	−1.40 ± 0.47	−2.97	0.0326	↓	Poorer insight was associated with lower social-cognitive ability
Social Cognition (T-score)	BABS Explanation of Differing Views (x3)	−6.90 ± 2.44	−2.82	0.0430	↓	Reduced metacognitive flexibility was associated with lower social cognition
Social Cognition (Percentile)	Y-BOCS Interference from	−11.41 ± 3.68	−2.97	0.0079	↓	Greater obsessional interference was

MATRICS Domain	Clinical Predictor	β (± SE)	t	p adj (Holm)	Direction	Interpretation
	Obsessions (x5)					associated with poorer social cognition
Visual Learning (Percentile)	Y-BOCS Distress Associated with Obsessive Thoughts (x4)	−11.19 ± 4.27	−2.62	0.0423	↓	Emotional distress from obsessions appeared associated with worse visual learning
Attention/Vigilance (T-score)	Education (High vs Low)	+22.44 ± 2.93	7.66	0.0415	↑	Higher education was associated with better sustained attention

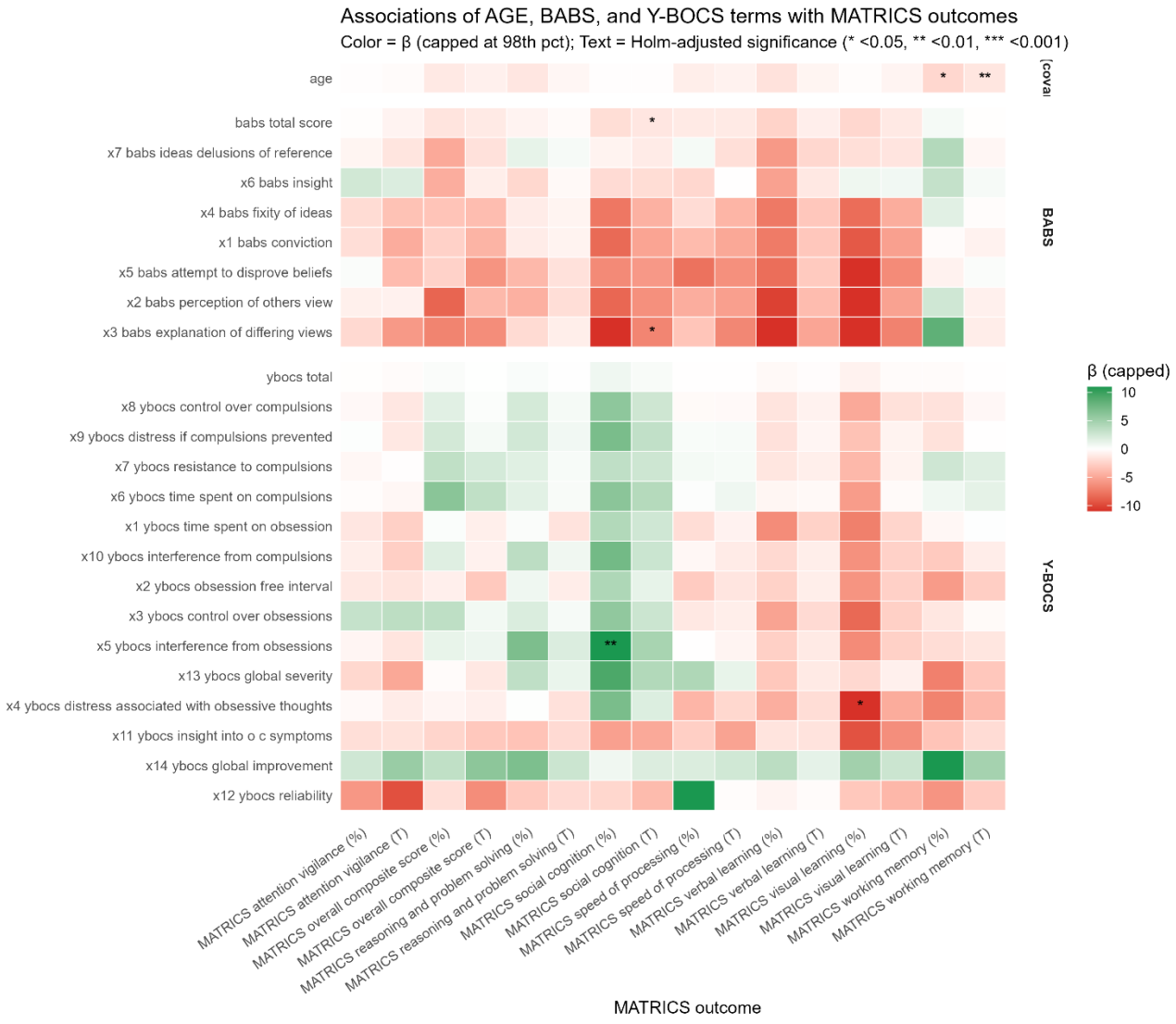

Figure 22. Heatmap describing the main result of the simplified model exploring the association between MATRICS-defined cognitive functions, age, BABS and YBOCS total scores and subcomponents.

All remaining Y-BOCS and BABS subcomponents exhibited consistent negative β coefficients, suggesting that both greater obsessional load and poorer insight tend to relate to lower cognitive efficiency, although not all survived correction. In Figure 22, each cell represents the standardised regression coefficient (β) from linear models adjusted for age and education. Warmer (red) tones indicate negative associations, cooler (green) positive ones. Coefficients are capped at the 98th percentile for visual contrast. Asterisks denote Holm-adjusted significance (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$*).

Rows correspond to individual BABS and Y-BOCS items or total scores; columns correspond to MATRICS domains (T-scores or percentiles).

Considering the potential impact of percentiles of extreme distributions in small samples, the results surrounding T-scores should be peferable as less prone to this effect. None of the tested biomarker survived Holm correction. For the uncorrected model there was a trend for some associations in the proposed model.

Nominal trends (uncorrected $p < 0.10$) included:

BDNF_z → Working Memory (percentile): $\beta = -35.4 \pm 11.9$, uncorrected $p = 0.045$ (Holm ns)

BDNF_z → Visual Learning (percentile): $\beta = -17.4 \pm 6.0$, uncorrected $p = 0.049$ (Holm ns)

TNF-α_z → Attention/Vigilance (T): $\beta = +6.97 \pm 2.38$, uncorrected $p = 0.071$ (Holm ns)

CRP_z → Attention/Vigilance (percentile): $\beta = +6.15 \pm 1.99$, uncorrected $p = 0.082$ (Holm ns)

These small-to-moderate effects did not remain significant after correction, indicating that biological covariates did not appear meaningfully associated with cognitive performances in our model. Consistent with expectations, age correlated negatively with Speed of Processing ($r = -0.42$, $p < 0.01$) and Working Memory ($r = -0.35$, $p = 0.02$). Higher education predicted superior Attention/Vigilance ($\beta = +22.44 \pm 2.93$, p adj = 0.0415). These covariates remained stable across both models, largely in line with our expectations.

4. Discussion

This study explored multilevel associations among clinical characteristics, cognitive performance, and peripheral biomarkers in OCD, focusing on diagnostic subtypes characterized by late onset (LO) and poor insight (PI). Three complementary analytical strategies comprising dimensionality reduction (PCA), unsupervised clustering, and supervised classification were applied to a multimodal dataset encompassing psychometric, neurocognitive, polysomnographic recordings, and peripheral biomarker domains. Principal Component Analysis revealed two primary latent dimensions explaining approximately one-third of the total variance. The first component (PC1) was dominated by cognitive and insight-related variables, including BABS Conviction and Explanation of Differing Views, Y-BOCS Control over Obsessions/Compulsions, and MATRICS learning and working-memory indices. The second component (PC2) focused on sleep-related physiology, comprising REM duration, sleep efficiency, oxygen desaturation index, and arousal indices and represented a sleep–arousal regulation dimension. Despite PC2 explaining a smaller proportion of variation, these results appear largely in line with previous evidence as eloquently reported from Nota et al, indicating that individuals with OCD display significant alterations in both sleep architecture and circadian regulation, including shorter total sleep time, increased nocturnal awakenings, and a higher prevalence of delayed sleep phase disorder.[44] Considering the naturalistic design of the study, it was not possible to control for potential confounders such as the specific pharmacological agents or their dosages, which may substantially influence sleep architecture and are often prescribed with differing frequency depending on individual clinical features. Contrary to our expectations, we found no evidence for the subjective quality of sleep and cognitive performance. An additional prospect worth exploring may be represented by the association of cognition and polysomnographic patterns; however, this was not explored within this specific analysis. Polysomnography recordings and cognitive performances have been studied in association with lifetime suicide attempts or ideation.[45–49] The limited number of lifetime suicide attempts in our sample (n=6) virtually prevented us from doing any meaningful analysis on this regard. The results of the PCA and the regression analysis appear to further corroborate the potential association for social cognition and insight.[1] Lower levels of BABS-defined insight total score and specifically the subcomponent related the specific Item 3 “Explanation of Differing Views” demonstrated a significant association even when correcting for multiple comparisons and

for the effect of age and education level.

In our study we found no significant association for the three selected candidate biomarkers and MATRICS-defined cognitive performances. We found a tendency for an association for uncorrected models between peripheral biomarkers and several cognitive domains, and more specifically between BDNF_z and working-memory or visual-learning percentiles, but these effects did not survive correction for multiple testing. These results need to be considered in the context of several limitations. The overall study sample comprised individuals of differing ages, comprising individuals in the developmental ages and spanning 5 to 79 years. It is plausible that differing levels of biomarkers or even their eventual associations with psychopathology or human pathology in general may vary depending on the life phase, and therefore, even selecting the subgroup with the most similar age range (e.g., PI and LO) and accounting for age, we could not find a significant relation between the studied variables. We did not account for the pro-BDNF/BDNF ratio, and therefore we cannot rule out that, more than the absolute level of this candidate biomarker, the ratio between these apparently opposing in effect biomarkers may be better informative for human pathology [50]. As highlighted by recent meta-analytic reviews [37], plasma-based, isoform-resolved, and drug-free assessments provide the most reliable signal. Ideally, future replications should consider implementing these optimized conditions, but these are not always easily achievable in an observational context. As noted in previous parts of the present report, considering the naturalistic nature of this study, a drug-free analysis would have been a difficult proposition. The conservative approach applied, aiming at reducing as much as possible the risk for false positive associations, might also have somewhat hindered our capacity to detect a signal. We cannot, however, rule out that the pharmacological therapy practised for psychiatric and general medical conditions alike might have influenced our results and potentially reduced our ability to detect meaningful differences among study groups. Insight has long been reported as a significant element in gauging OCD severity, with lower insight reported as predicting, in general, lower response to selective serotonin reuptake inhibitors in OCD[51], with a more nuanced association with response for psychotherapy, depending on whether we consider pediatric or adult OCD. In pediatric OCD, psychotherapy such as cognitive behavioural therapy appears to show no impact on baseline insight in OCD patients, potentially underscoring

differences between adult and pediatric patients even in terms of treatment response.[51] Second-generation neuroleptics are frequently proposed to patients with poor insight as augmentation to regular first-line medications, with good evidence of effectiveness in treating refractory cases, ranging from 40% to 55%.[52] The significant metabolic impact of these medications may further represent one layer of complexity in interpreting our results, also on cognitive functions, both with regard to a direct effect of these medications on cognition, sleeping patterns, metabolic parameters, and indirectly through increased weight gain, for instance. This element was not fully accounted for in our machine-learning protocol and should therefore be considered a potential limitation of the present analysis. Similarly, the level and frequency of sedating agents were also not accounted for in our analysis, and there was no attempt at balancing recruitment efforts across categories to account for this confounding. We found evidence for significant discriminatory contribution for BABS conviction and total score as the most significant contributing factor in differentiating LO and PI. This appears hardly surprising, given the potential collinearity between the definition of PI and the level of BABS-assessed insight. Tulaci et al[53] report on the interplay between the capacity to understand other individuals by ascribing mental states as defined according to the theory of mind (TOM) and insight in obsessive compulsive disorder, finding that OCD subjects in general have worse performances in TOM skills as compared with healthy controls and that TOM skills tend to negatively correlate with BABS-total scores. The integration of machine-learning methods in psychiatric research has so far enabled data-driven characterisation across multiple dimensions of empirically defined multidimensional phenotypes, far beyond what is typically achieved in the classical categorical framework. In the present study, we applied both supervised and unsupervised methods, and our results appear to suggest that insight and sleep physiology may be the most relevant elements in capturing interindividual heterogeneity in our sample. It is the opinion of the writer that, despite the aforementioned limitations, our results may posit polysomnography as a particularly interesting substrate for this type of approach. Social cognition has been explored in the past in association with sleep patterns, with sleep chronotypes being, for instance, associated with different types of response to social stimuli. In this context, the strong performances for the supervised classifier (e.g., F1 0.9) may suggest that non-linear combinations of cognition, inflammatory and sleep-related variables may

provide valuable diagnostic information, otherwise lost in classical statistical modeling. These elements could be capitalized in population stratification for subject recruitment in clinical trials specifically investigating the effect on clinical outcomes for sleep-targeted interventions such as CBT-I or chronotherapy in OCD. Fewer studies have investigated the possible interplay between social cognition and sleep in OCD. The impact on specific cognitive performances or insight for individuals featuring prominent sleep problems is unclear but worth exploring, considering the available evidence. Ultimately, integrating machine learning approaches in adequately powered longitudinal studies may further enhance our understanding of the potential interplay between inflammation, sleep disorders, cognition and psychopathology at large and with a focus on OCD. MSCEIT MATRICS-subtask offers a quantifiable window in social-affective cognition. As reported in the prior part of the present document, recent studies exploring dynamic assessments of social cognition in OCD applying tools such as the Movie for the Assessment of Social Cognition (MACS) suggest that a deficit in mentalization may be associated with aggressive and harm-related obsession.[2] The potential for further subtyping and stratifying the OCD population is still to be fully explored. Mentalization networks, including the amygdala, anterior cingulate cortex, and insula, may represent additional targets for functional and structural imaging, to be integrated with polysomnographic and clinical assessments for machine-learning-guided biomarker discovery. Given prior evidence that OCD may involve abnormal activation of social and emotional processing circuits,[2] machine learning approaches trained on multimodal data integrating polysomnographic patterns and social cognition measures could further elucidate latent affective-cognitive interactions underlying maladaptive patterns of social interaction. Considering the foregoing, we humbly suggest that our results may represent a valuable addition to the field and a platform for further discoveries in OCD phenotyping.

5. Conclusions

In conclusion, while peripheral biomarkers showed only nominal relationships with cognition, behavioral markers of the applied insight measures defined according to the BABS, especially the ability to explain others' differing views, emerged as a salient correlate of social-cognitive

performance. This finding appears largely in line with the existing literature and further strengthens the impression that insight in OCD, far from representing a unitary construct, may be more realistically conceptualized as a composite measure of belief conviction, evaluative flexibility, and social perspective-taking. The tested translational biomarkers such as BDNF, TNF-α, and CRP may still represent valuable options to explore, but within the limits of our analysis, we found no evidence to support their use in OCD phenotype within the selected framework, nor did we find significant associations with MATRICS-defined cognitive profiles.

6. References

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