A New Conceptualization of the Psychopathology in Schizophrenia by Non-negative Matrix Factorization

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Brain & Behaviour

Introduction

●Schizophrenia (SCZ) is **heterogeneous** [1] with marked inter-individual variability of psychopathology. Low-rank dimensional representations of SCZ psychopathology and clinical subtypes, however, have been a continued matter of conjecture.

●A novel parts-based learning approach of orthonormal projective non-negative matrix factorization (OPNMF) [2] was employed, upon which patients were clustered into psychopathological subtypes. Finally, psychopathological subtypes were classified based on resting-state fMRI functional connectivity.

●**Aim: To provide**

➢ **a cross-validated and generalizable factor model as a low-rank representation of SCZ psychopathology;**

➢ **a reliable SCZ subtyping;**

➢ **neurobiological substrates of the identified psychopathological subtypes**

Methods

●**Study population**

Patients from 11 medical centers/universities with 30 individual-item PANSS scores:

One homogeneous sample of **1545** patients from the north of the Netherlands (PHAMOS).

One heterogeneous dataset with **490** patients from 10 sites located in Europe, the USA and Asia.

●**PANSS factorization by OPNMF**

➢ **OPNMF owes advantages of a) sparse and b) projectable,** which solves the below energy minimization problem:

$$\underset{\mathbf{W}\geq 0,\mathbf{H}\geq 0}{\text{minimize}}\ \mathcal{J}_F^{\perp}(\mathbf{W},\mathbf{H}) = \|\mathbf{X}-\mathbf{W}\mathbf{H}\|_F^2 \quad \text{subject to} \quad \mathbf{H}=\mathbf{W}^T\mathbf{X},\ \mathbf{W}^T\mathbf{W}=\mathbf{I}$$

W: basis matrix (dictionary) with each column encoding a factor; H: loading matrix, represented by the projection of V onto W:

➢ **Model evaluation and selection**

Factor-solutions were evaluated in two aspects:

1. stability (by measuring adjusted rand index, variation of information and concordance index)

2. generalizability (by measuring transfer reconstruction errors)

● **Psychopathological subtypes**

➢ Fuzzy c-means was used to cluster patients based on the factor-loadings

- Fuzzy silhouette index, Xie and Beni index and partition entropy were employed to determine the optimal cluster number
- Stability was evaluated by a leave-one-site out analysis, as well as subsampling and bootstrap resampling strategies

➢ Ambiguously assigned patients were removed deriving the "core" subtypes

● **Predicting psychopathological subtypes from resting-state fMRI connectivity patterns**

➢ Resting-state functional connectivity matrix was constructed based on a 600 parcellation scheme

➢ Radial Basis Function (RBF) kernel based support vector machine (SVM) was used

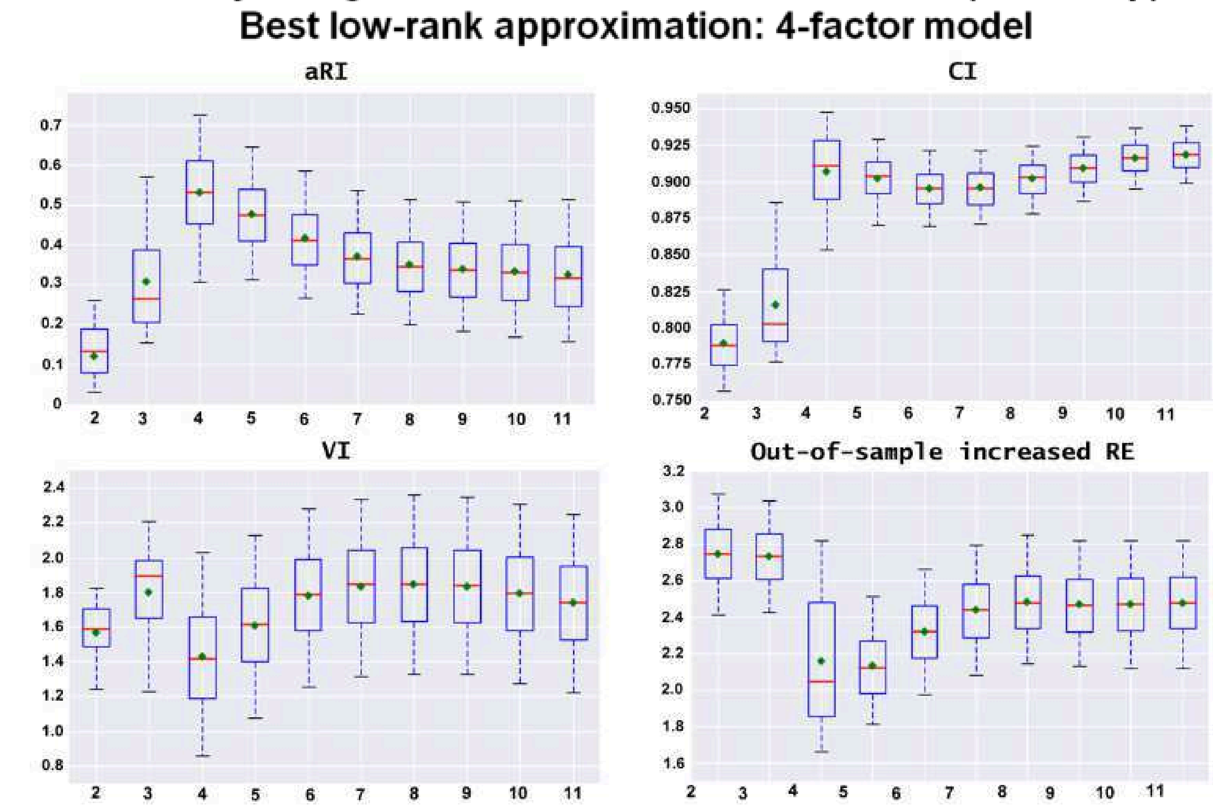
➢ A grid-search scheme was implemented to tune the two hyperparameters of C and γ

➢ A permutation test to assess whether the parcel-wise accuracy was significantly above chance

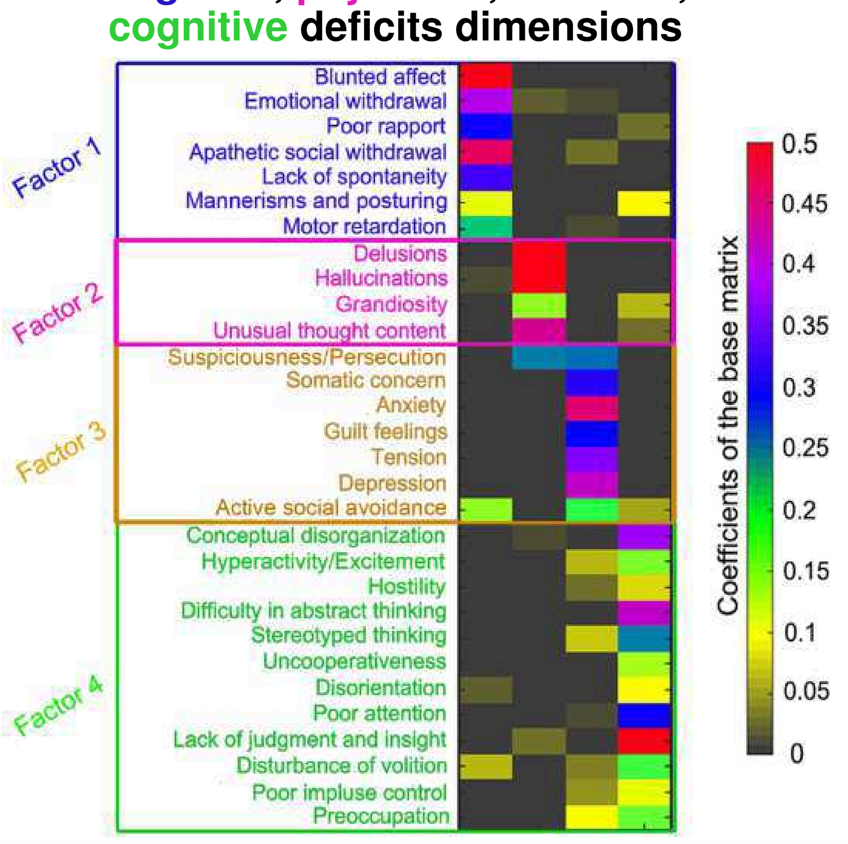
Results

1. PANSS factorization

Stability and generalization across the datasets (bootstrap)
Best low-rank approximation: 4-factor model



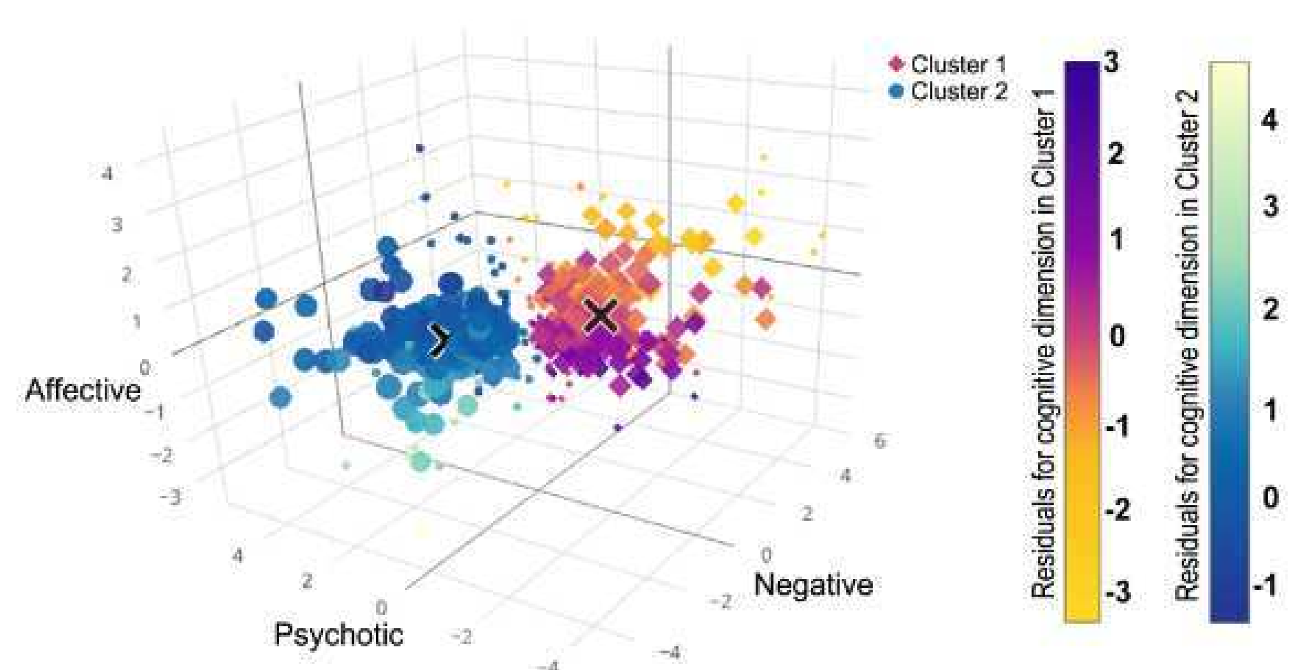
The final 4-factor model (PHAMOS): Negative, psychotic, affective, cognitive deficits dimensions



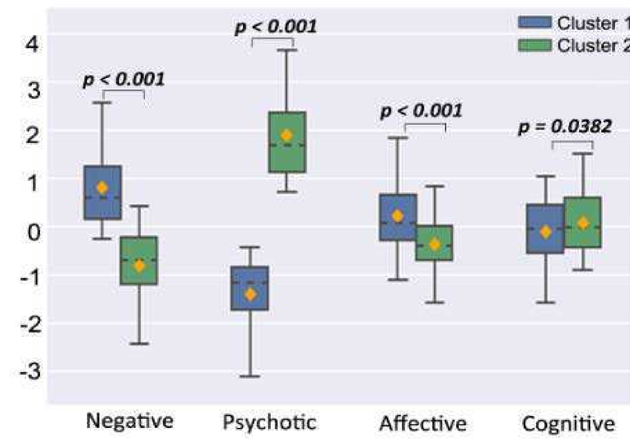
➢Higher aRI (adjusted rand_index) and CI (concordance index): higher stability
➢Lower VI (variation of information) and RE (error-increase): better generalization

2. Psychopathological subtypes

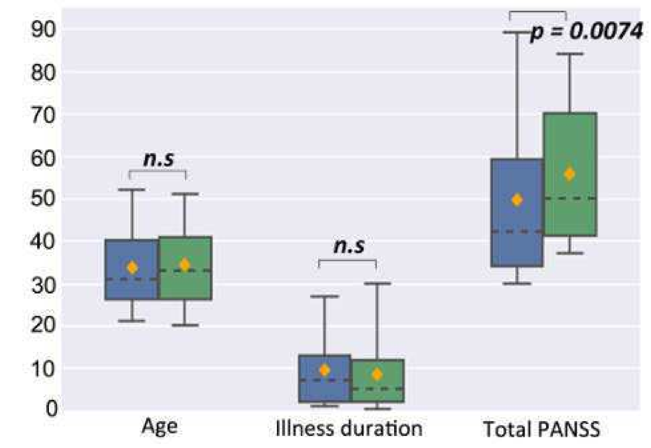
A. 4D visualization of the two clusters (outliers were defined by membership values < 0.7 and were shown in small dots, X represents the centroid)



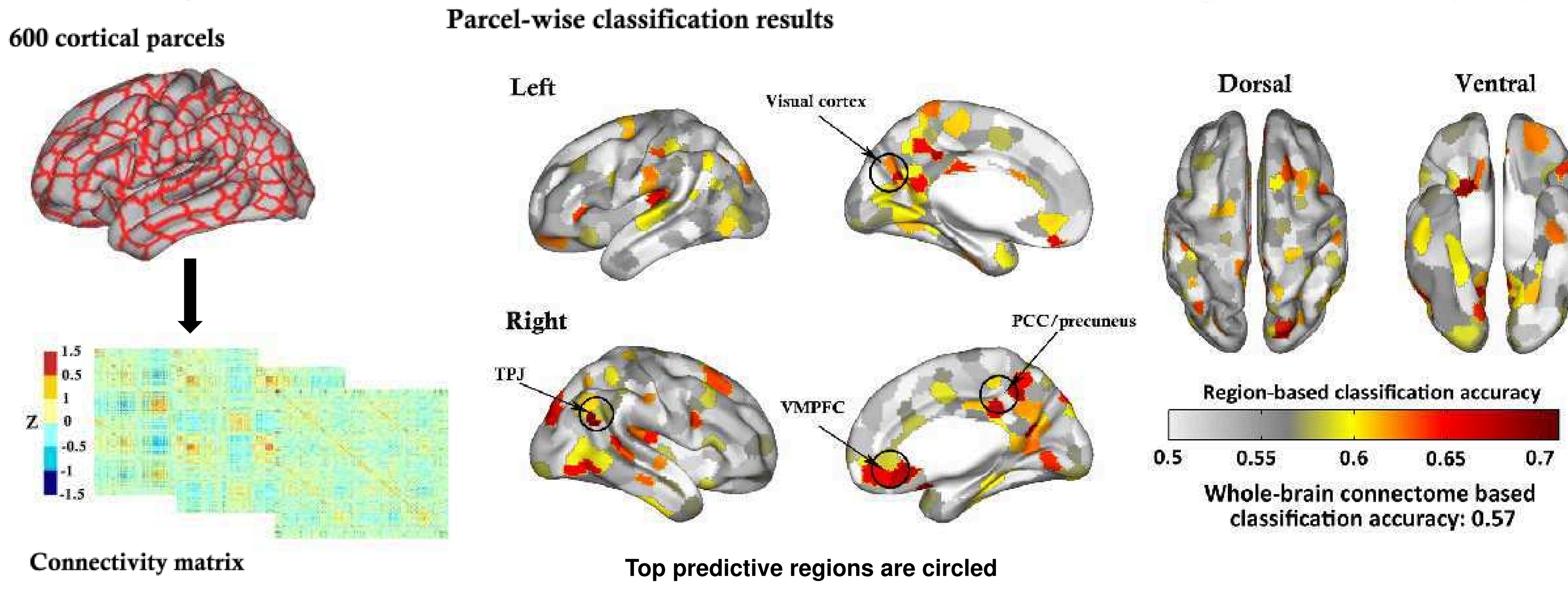
B. Comparison of the four factor-loadings between the two "core" subtypes



C. Comparison of age and clinical features between the two "core" subtypes



3. Predicting psychopathological subtypes from resting-state fMRI connectivity



Discussion

1. A 4-factor model was found to be optimal. It matches with previous studies [3] and accommodates variable degrees of psychotic symptoms across a large range of populations, settings, and medical systems.
2. Previous clinical subtypes [4,5] vary in numbers and definitions. Nonetheless, a positive-negative dichotomy has been widely supported [6]. Here we emphasized that a stable and replicable dichotomous sub-typing can be derived upon the 4 psychopathological dimensions.
3. Region-wise classification out-performed whole-connectome based classifier. The top predictive regions are all supported by previous literature [7]. The highest accuracy revealed here was fairly comparable to previous classification that discriminated SCZ patients from healthy subjects [8].

The current study provides a novel cross-validated, generalizable low-rank approximation of SCZ psychopathology based on more than 1500 patients. Based on this optimal factor-structure, a reliable "core" psychopathological sub-typing was proposed which could be predicted from resting-state functional connectivity with a high accuracy.

References:

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