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From cognitive and clinical substrates to functional profiles: Disentangling heterogeneity in schizophrenia

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ABSTRACT

The relationship between neurocognition and functioning among patients with schizophrenia is well documented. However, integrating neuropsychological, clinical and psychopathological data to better investigate functional outcome still constitutes a challenge. Artificial neural network-based modeling might help to better capture clinical heterogeneity by analyzing the non-linear relationships among multiple variables. Two hundred and fourteen clinically stabilized patients with schizophrenia were recruited and assessed for neurocognition, psychopathology and functioning. Artificial neural network analyses were conducted to yield significant predictors of functional outcome among clinical and cognitive variables and to build distinct functional Profiles, each characterized by a different medley of cognitive and clinical features. Twenty-two key predictors of daily functioning emerged, encompassing neurocognitive and clinical domains, with major roles for processing speed and attention. Four Profiles were constructed based on specific levels of functioning, each characterized by a distinct distribution of key clinical and neurocognitve measures. This study highlights the importance of a more in-depth investigation of cognitive and clinical heterogeneity. A better understanding of the building blocks of these Profiles would lead to more individualized rehabilitation treatments.

1. Introduction

Schizophrenia constitutes a multidimensional psychiatric condition exhibiting high heterogeneity (both between- and within-subjects) as one of its core features. The issue of chronic functional disability among patients has gained increasing attention, in so far that new treatment models have been proposed. For example, the functional recovery model (i.e. the acquisition of meaningful roles in the community) suggests a shift in clinical practice by focusing on restoring good levels of functioning, rather than on a complete remission of symptoms (Harvey and Bellack, 2009). Accordingly, the multiple factors determining functioning became the targets of therapeutic interventions (Buonocore et al., 2013; Lepage et al., 2014). Therefore, research focused on the possible contributing factors, especially cognitive impairment, positive and negative symptomatology and disease's course (Bechi et al., 2017; Mantovani et al., 2015; Menendez-Miranda et al., 2015).

More specifically, although previous studies have identified the roles of psychopathological, environmental and demographic variables, neurocognition turned out to be the most significant predictor of functional (Bechi et al., 2017; Bryce et al., 2016; Green and Harvey, 2014; Keefe et al., 2016) and psychosocial outcome (Galderisi et al., 2013). Consequently, neuropsychological impairment has become an important target of both therapeutic and rehabilitative interventions, which aim at maximizing achievable improvements, stabilization and generalized benefits (Cavallaro et al., 2009; Wykes and van der Gaag, 2001).

However, when considering neurocognition only, it is not possible to capture the whole heterogeneity that characterizes schizophrenia outcome and a significant percentage of variance remains unexplained. Thus, integrating neuropsychological, clinical and psychopathological data in order to better investigate functional outcome still constitutes a challenge, with crucial implications on both clinical and research settings. This issue is also supported by the presence of contrasting evidence in literature. A possible explanation might be due to methodological differences between studies, as well as the different sets of

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variables that are manipulated among research protocols. For example, Galderisi and colleagues (Galderisi et al., 2014) in a recent work addressing predictors of real-life functioning, while confirming the role of neurocognition, also highlighted that the effects of the main predictors of functional outcome were not as straight-forward as expected. Moreover, as far as clinical practice is concerned, it is not unusual to find out patients exhibiting either a global neurocognitive profile within normal ranges (Leung et al., 2008), or a combination of cognitive features, including “cognitive-normal range” and “below-normal range” domains (Chiang et al., 2016). In other words, patients’ neuropsychological status shows a great heterogeneity both within-subjects (i.e. an individual's cognitive process like attention might be severely impaired, while another like working memory might be efficient) and between-subjects (i.e. each individual might exhibit a specific medley of cognitive strengths and weaknesses, different from that of other patients).

In summary, the relationship between schizophrenia symptomatology and neuropsychological status seems to be highly complex and probably characterized by non-linearity, since there are patients showing symptoms with and without cognitive or functional impairments, and patients exhibiting no symptoms with and without cognitive or functional impairments as well. Functional outcome thus derives from the interplay among multiple variables (clinical, neurocognitive, demographic, environmental), which must be addressed simultaneously in order to better investigate functional disability among patients.

Given this scenario, traditional (linear) statistical approaches may not properly capture heterogeneity. Computational modeling tools, designed as an artificial intelligence analog of biological nervous systems, such as Artificial Neural Networks (ANNs) may be better suited (Szaleniec, 2012). ANNs present several advantages: first, their information processing characteristics; second, their high parallelism, fault and noise tolerance; third, their ability to learn from examples and their generalization capacities (Basheer and Hajmeer, 2000). In other words, ANNs help to elucidate the underlying relationships between input and output, regardless of the problem's dimensionality and of the system's non-linearity. Over time, innovative applications of ANN theory have been successfully explored, even in Biology (Szaleniec, 2012) and Psychiatry (Adams et al., 2016; Lin et al., 2008; Prieto et al., 2016; Schmidhuber, 2015), although caution is always required (Takahashi et al., 2010).

This study aims to further investigate, through an innovative approach, the relationships between multiple variables (i.e. the main psychopathological, neurocognitive and clinical predictors of functional outcome) and daily functioning in a sample of patients with schizophrenia. In addition, this work aims to construct several Profiles, which would describe typical patterns of interaction among variables and capture clinical heterogeneity as well.

2. Methods

2.1. Subjects

214 subjects (M:F = 134:80) with a diagnosis of DSM-IV-TR schizophrenia were recruited from the Department of Clinical Neurosciences of IRCCS San Raffaele Scientific Institute, Milan. All diagnoses were certified by trained psychiatrists, by means of the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-1) (First et al., 1997). To be eligible for enrollment, patients had to have been on a stable dose of antipsychotic therapy for at least 6 months. Exclusion criteria were: co-morbid diagnosis on Axis I or II, substance dependence or abuse in the past year, major neurological illness and perinatal trauma. Written informed consent was provided by all patients. The protocol followed the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

Demographic and clinical data were collected and the following functional, psychopathological and neuropsychological assessments were administered by trained rehabilitation therapists, psychiatrists and psychologists, respectively.

2.2. Assessment

2.2.1. Functional assessment

2.2.1.1. Quality of Life Scale (QLS). Daily functioning was assessed by the Quality of Life Scale (QLS) (Heinrichs et al., 1984), a 21-item semi-structured interview balancing subjective questions regarding life satisfaction and objective indicators of social and occupational role functioning. QLS represents a measure of the level of everyday abilities, strongly correlated to assessment of more objective functioning Schizophrenia Objective Functioning Instrument (SOFI). A global score of daily functioning is provided.

2.2.2. Psychopathological assessment

2.2.2.1. Positive and Negative Syndrome Scale (PANSS). The presence and the severity of symptoms was evaluated by using the PANSS (Kay et al., 1987), a 30-item scale. It consists of three subscales measuring positive and negative symptoms, as well as general severity of illness.

2.2.3. Neuropsychological assessment

2.2.3.1. Brief Assessment of Cognition in Schizophrenia (BACS). The BACS (Keefe et al., 2004) assesses the aspects of cognition found to be most impaired and most correlated with outcome in patients with schizophrenia. Since it has been translated, the Italian version with normative data on the healthy population has been used (Anselmetti et al., 2008). It consists of six subtests: list learning (verbal memory), digit sequencing task (working memory), token motor task (psychomotor speed and coordination), categorical instances and controlled oral word association test (verbal fluency), symbol coding (selective attention and speed of information processing) and Tower of London (planning). Two alternate versions (A and B) are available for those subtests which are more sensitive to learning effect.

2.2.3.2. Wisconsin Card Sorting Test (WCST). The WCST (Heaton, 1981; Milner, 1963) provides a measure of executive functioning. Subjects are invited to sort all the cards from two decks according to different criteria and have to learn which specific one is required on the basis of the examiner's feedbacks. The criterion is changed after ten consecutive correct answers. Perseverative errors are made when subjects persist in applying a previous criterion, once it has been changed, and provide a measure of cognitive flexibility. In this study, a computerized version of the WCST was administered (Bustini et al., 1999; Stratta et al., 1997).

2.2.3.3. Continuous Performance Test (CPT). The CPT (Rosvold et al., 1956) provides a measure of attention, both selective (i.e., false alarms and correct hits) and sustained (i.e., the number of missed targets and correct hits). The A-X version, modified by Stratta et al. (2000), was administered. Subjects are shown letters which appear serially on a screen for 200 msec. They have to press a key only when the letter X follows the letter A. Acoustic feedback is provided. In this study, the number of missed targets was considered for analysis, too.

2.2.3.4. Wechsler Adult Intelligence Scale-Revised (WAIS-R). Intelligence was assessed by the WAIS-R (Wechsler, 1981), a composite scale which includes both verbal and performance subtests on alternate order. The WAIS-R provides a verbal IQ, a performance IQ and a total IQ measure.

2.3. Statistical analyses

2.3.1. ANN analyses

The present study's statistical approach included both preliminary and principal ANN analyses. Preliminary analyses aimed at identifying the best ANN configuration, as well as the significant predictors of

functional outcome. Subsequently, principal analyses aimed at identifying possible Profiles, whose structure relied on different levels of functioning. More in detail, Intelligent Problem Solver (IPS) was performed in order to identify the best network performance, and Pruning Algorithm and Sensitivity Analysis were launched to extract the key variables predicting daily functioning. Afterwards Profiles were identified by using Kohonen networks.

2.3.1.1. Preliminary analysis: IPS. IPS performs a data selection approach through supervised learning algorithms (Basheer and Hajmeer, 2000; Szaleniec, 2012). This process generates thousands of ANNs in order to find the best configuration to solve the target problem. Thus, IPS was set to optimize the initial population including all the clinical and neuropsychological variables, with functional outcome as the output variable. The tested ANN configurations were Multi-Layer Perceptrons (MLP) and Radial Basis Functions (RBF).

2.3.1.1.1. MLP. MLPs are feed-forward networks of graded-response "neurons" (Prieto et al., 2016). A "neuron" represents the elementary unit in the artificial neural network so named due to its similarity to the actual biological neurons. More specifically, in artificial neurons, the dendrites represent the input vector performing multiplication by that dendrite's "weight value." The soma represents the summation function of inputs from dendrites, while the axon will receive the summation from the soma and transmit the signal, connecting one artificial neuron to other artificial neurons. Artificial neurons are usually aligned in three layers: input, hidden, and output neurons (Szaleniec, 2012). The hidden neurons of the second layer process the information received from the input neurons and pass them over to neurons of the output layer (Basheer and Hajmeer, 2000). The hidden layer constitutes the most important part of the network: in fact, each neuron of this layer collects the signals from all of the input neurons and produces various levels of activation as an output. The final signals are hence collected in the output neurons, which produce the predicted value as its output (Szaleniec, 2012).

2.3.1.1.2. RBF. RBFs constitute a special case of feedforward error-backpropagation networks with three layers. The hidden layer clusters the inputs of the network; the neurons belonging to this layer are called cluster centers (Basheer and Hajmeer, 2000). RBFs are based on a kernel method which frequently uses Gaussian functions (Prieto et al., 2016).

2.3.1.2. Preliminary analysis: Pruning Algorithm and post-processing Sensitivity Analysis. After IPS, a Pruning Algorithm and a Sensitivity Analysis were implemented to extract the key variables predicting daily functioning (Mulsant, 1989). As far as Sensitivity Analysis is concerned, the initial network is trained, and the influence of a particular input variable is assessed on the basis of the ratio of error calculated for models with and without that variable. If the prediction of ANN improves after the removal of a particular descriptor, the variable can be safely removed without compromising the ANN prediction capabilities (Szaleniec, 2012).

2.3.1.3. Definition of profiles: Kohonen network. Kohonen networks are two-layered and transform an *n*-dimensional input space onto lower-ordered data (i.e., a 2D map of a Kohonen neuron), where similar patterns project onto points in close proximity to one another (Kohonen, 1989; Szaleniec, 2012). Kohonen networks are trained in an unsupervised manner in order to form clusters within the data, grouping them based on similarity or dissimilarity (Basheer and Hajmeer, 2000). In other words, Kohonen networks build Profiles of interaction among variables.

Table 1
Clinical-demographic data.

	Mean score	SD
N	214	
Sex	134 M	80 F
Age	34.58	9.70
Education	10.83	2.97
Onset	23.46	5.70

3. Results

3.1. Descriptive analyses

Clinical-demographic information were collected for each patient, with particular attention to: age, sex, education, diagnostic subtype and age of onset (see Table 1). Diagnostic subtypes were distributed as follows: paranoid (43.48%); disorganized (13.77%); undifferentiated (42.75%). The majority of patients was receiving atypical antipsychotic medication (30.69% risperidone, 47.52% clozapine, 7.92% olanzapine, 0.99% aripiprazole). A small percentage of subjects was receiving typical antipsychotic medication (12.87% haloperidol). Mean scores and standard deviations of functional, psychopathological and neuropsychological assessments are reported in Table 2.

3.2. ANN analyses

3.2.1. Preliminary analyses

As detailed above, the key variables predicting functional outcome were identified and extracted by preliminary ANN analyses (i.e., IPS, Pruning Algorithm and Sensitivity Analysis). More in detail, IPS performed neural algorithms optimization runs (i.e., MLP and RBF). A three-layer MLP with a margin of error: 0.31, 26 neurons in the input layer, 10 neurons in the hidden one, and a regression ratio: 0.41 represented the best performance. The tested networks overall achieved an excellent performance with a regression ratio: 0.41; a correlation value: 0.91 and a margin of error: 0.31. The implementation of the

Table 2
mean scores of functional, psychopathological, clinical and neurocognitive measures.

	Mean	SD
N	214	
QLS-Total	54.56	23.91
PANSS-Positive	15.83	8.76
PANSS-Negative	20.30	7.85
PANSS-General	32.88	10.40
PANSS-Total	69.19	21.74
IQ-Verbal	87.21	13.52
IQ-Performance	81.02	14.14
IQ-Total	83.43	18
Correct Sequences (WM)	16.50	4.93
Sequence Length (WM)	6.28	2.20
Token (Motor Coordination 30")	34.90	34.12
Token (Motor Coordination 60")	68.64	18.36
Phonological Fluency	9.94	4.57
Semantic Fluency	16.13	6.69
Symbol Coding (Processing Speed)	38.05	12.53
Tower of London (EF)	13.21	5.31
List Learning (Verbal Memory)	34.53	10.70
Perseverative errors - WCST (EF)	16.41	11.24
Hits - CPT (Sustained Attention)	140.07	36.48
False alarms - CPT	7.72	13.76
Distractions - CPT	8.33	14.82
Missed – CPT	36.98	34.67

QLS: Quality of Life Scale; PANSS: Positive and Negative Syndrome Scale; IQ: Intelligence Quotient; WM: Working Memory; EF: Executive Functions; WCST: Wisconsin Card Sorting Test; CPT: Continuous Performance Test

Table 3
Key variables extracted by the Pruning Algorithm and the Sensitivity Analysis, ordered by ranks.

Symbol Coding (Processing Speed)	RANK: 1 ERROR: 0.6444448 Ratio: 1.877327
Male (Gender)	RANK: 2 ERROR: 0.531004 Ratio: 1.546862
Missed Targets - CPT (Sustained Attention)	RANK: 3 ERROR: 0.472112 Ratio: 1.375306
Verbal Memory	RANK: 4 ERROR: 0.463724 Ratio: 1.350871
Hits - CPT (Sustained Attention)	RANK: 5 ERROR: 0.458162 Ratio: 1.334668
Diagnostic subtype	RANK: 6 ERROR: 0.4463804 Ratio: 1.300347
Semantic Fluency	RANK: 7 ERROR: 0.44172 Ratio: 1.286771
PANSS -Total	RANK: 8 ERROR: 0.431831 Ratio: 1.257962
IQ-Total	RANK: 9 ERROR: 0.413244 Ratio: 1.2203819
Education	RANK: 10 ERROR: 0.405684 Ratio: 1.181795
Correct Sequences (WM)	RANK: 11 ERROR: 0.3965575 Ratio: 1.155208
Age	RANK: 12 ERROR: 0.387451 Ratio: 1.12868
Tower of London (EF)	RANK: 13 ERROR: 0.386171 Ratio: 1.124953
Token (Motor Coordination 30")	RANK: 14 ERROR: 0.384931 Ratio: 1.12134
Perseverative Errors - WCST (EF)	RANK: 15 ERROR: 0.3837616 Ratio: 1.117933
Sequence Length (WM)	RANK: 16 ERROR: 0.3719691 Ratio: 1.08358
PANSS-Negative	RANK: 17 ERROR: 0.3689107 Ratio: 1.074671
Token (Motor Coordination 60")	RANK: 18 ERROR: 0.363502 Ratio: 1.058913
Antipsychotic Therapy	RANK: 19 ERROR: 0.362695 Ratio: 1.056563
Phonological Fluency	RANK: 20 ERROR: 0.360351 Ratio: 1.049735
IQ-Verbal	RANK: 21 ERROR: 0.346794 Ratio: 1.010242
IQ-Performance	RANK: 22 ERROR: 0.344713 Ratio: 1.004181

PANSS: Positive and Negative Syndrome Scale; IQ: Intelligence Quotient; WM: Working Memory; EF: Executive Functions; WCST: Wisconsin Card Sorting Test; CPT: Continuous Performance Test.

Pruning Algorithm extracted 26 variables. Then, a further selection was performed by Sensitivity Analysis, which identified 22 key variables, ordered by ranks in descending order of importance. As reported in Table 3, the key predictors included cognitive, psychopathological, as well as socio-demographic features.

3.2.2. Identification of functional profiles

Principal analyses (i.e., Kohonen networks) were performed to construct Profiles characterized by different levels of the key variables (i.e., predictors of functional outcome), which would rely in turn on different levels of functioning, based on QLS cut-off scores derived from the analyses. In other words, each Profile would exhibit a unique medley of distribution of the key cognitive, psychopathological and socio-demographic features with respect to the overall functional level. In more detail, the Kohonen network analyses revealed four self-organizing Profiles. As explained above, the Profiles' structure relies on different levels of functioning, based on QLS cut-off scores derived from the ANN analyses. Table 4 reports mean values and standard deviation of the key variables according to each level of functioning. In particular, Profile 1 included 39 subjects with a QLS total score between 0 and 30 (*M*: 23.72; *SD*: 6.07) and an action range between 20 and 30. Profile 2 comprehended 99 subjects with a QLS total score between 30 and 60 (*M*: 46.97; *SD*: 8.10) and an action range between 40.50 and 60, Profile 3 was made up of 59 subjects with a QLS total score between 60 and 90 (*M*: 72.73; *SD*: 9.20) and an action range between 64 and 90. Profile 4 included 17 subjects with a QLS total score between 90 and 120 (*M*: 105.88; *SD*: 8.71) and an action range between 100 and 120.

Especially noteworthy, as depicted in Table 4 a higher level of functioning did not necessarily correspond to higher average variable values: as far as top ranked variables are concerned, mean attention scores showed an irregular pattern among Profiles in particular CPT Hits scores. In fact, the maximum average value (144.28) associated with the lowest level of functioning (i.e. Profile 1). In contrast, Symbol Coding and Verbal Memory performances exhibited a "gradient pattern" among Profiles, with average values directly proportional to their relative level of functioning. Concerning Gender, fewer males were found in higher levels of functioning (i.e., Profiles 3 and 4). The distribution of Diagnostic Subtypes among the Profiles was also noted. Paranoid Schizophrenia was more frequent in higher levels of functioning. In contrast, Disorganized and Undifferentiated Schizophrenia turned out to be more frequent in lower levels of functioning. As far the other variables are concerned, several turned out to follow regular "gradient patterns" among Profiles, both directly and inversely proportional to their levels of functioning (i.e. Semantic Fluency, Correct Sequences, Tower of London, Sequence Length, Phonological Fluency, Education and Perseverative Errors on the WCST, PANSS Total Score, PANSS Negative Score, Antipsychotic Therapy-Olanzapine, respectively). However, slightly and markedly irregular patterns among Profiles also emerged (psychomotor coordination performance, all IQ measures, Age and Antipsychotic Therapy).

It was also possible to identify three Sub-Profiles, composed of 5, 13 and 15 "outlier" patients respectively, within Profiles 1–3. Such Sub-Profiles turned out to exhibit a homogeneous distribution regarding major rank variables (e.g., symbol coding, gender, verbal memory performance) with respect to their primary Profile category. However, the Sub-Profiles' distribution regarding minor rank variables (e.g., verbal and performance IQ) turned out to be significantly different when compared to their primary Profiles, but were more homogeneous to the distribution found in other primary Profiles. For example, Sub-Profile I showed a homogeneous pattern to Profile 1 in major rank variables while it exhibited similarity in minor rank variables to Profile 2; Sub-Profile II showed a homogeneous pattern to Profile 2 (major rank variables) and a tendency to Profile 1 (minor rank variables); and Sub-Profile III showed a homogeneous pattern to Profile 3 (major rank variables) and a tendency to Profile 4 (minor rank variables). In other words, there were subgroups of patients with a similarity to their primary Profile for its crucial features, but also a similarity to another Profile for less important features.

To end with, in order to summarize our results concerning Profiles 1–4, Chernoff Faces were plotted (see Fig. 1). The Faces' features

Table 4
Description of the profiles.

Main variables extracted (Ordered by ranks)	Profile 1	Profile 2	Profile 3	Profile 4
Symbol Coding (Processing Speed)	Mean score: 34.18 SD: ± 12.09 Action range: 26 → 63	Mean score: 36.49 SD: ± 12.38 Action range: 28 → 65	Mean score 41.73 SD: ± 12.17 Action range: 33 → 73	Mean score: 44.91 SD: ± 11.66 Action range: 22 → 52.9
Male (Gender)	M:TOT = 24:39 61.54%	M:TOT = 65:99 65.66%	M:TOT = 35:59 59.32%	M:TOT = 10:17 58.82%
Missed Targets - CPT (Sustained Attention)	Mean score: 33.52 SD: ± 28.59 Action range: 5.6 → 125	Mean score: 40.17 SD: ± 35.36 Action range: 10.25 → 157	Mean score: 33.76 SD: ± 37.58 Action range: 7 → 142	Mean score: 38.4 SD: ± 33.80 Action range: 12.4 → 112
Verbal Memory	Mean score: 31.14 SD: ± 9.55 Action range: 11 → 48	Mean score: 34.78 SD: ± 10.22 Action range: 27.75 → 59	Mean score: 35.65 SD: ± 12.39 Action range: 28 → 66	Mean score: 38.73 DS: ± 8.91 Action range: 32 → 57
Hits - CPT (Sustained Attention)	Mean score: 144.28 SD: ± 27.71 Action range: 58 → 179	Mean score: 138.10 Ds ± 38.69 Action range: 125 → 186	Mean score: 141.27 SD: ± 39.29 Action range: 13.08 → 45.31	Mean score: 138.53 SD: ± 32.56 Action range: 117 → 179
Diagnostic subtype	1: Paranoid 29.63% 2: Disorganized 22.22% 3: Catatonic 0% 4: Undifferentiated 48.15%	1: Paranoid 44.83% 2: Disorganized 12.07% 3: Catatonic 0% 4: Undifferentiated 43.10%	1: Paranoid 45% 2: Disorganized 12.5% 3: Catatonic 0% 4: Undifferentiated 42.5%	1: Paranoid 61.54% 2: Disorganized 7.69% 3: Catatonic 0% 4: Undifferentiated 30.77%
Semantic Fluency	Mean score: 14.05 SD: ± 6.12 Action range: 3.9 → 25	Mean score: 15.73 SD: ± 6.73 Action range: 15 → 45	Mean score: 17.12 SD: ± 6.57 Action range: 13 → 35	Mean score: 19.62 SD: ± 6.96 Action range: 14 → 28
PANSS -Total	Mean score: 81.5 SD ± 24.71 Action range: 57.4 → 150	Mean score: 72.43 SD: ± 17.52 Action range: 60 → 119	Mean score: 61 SD: ± 20.42 Action range: 46 → 106	Mean score: 47 SD: ± 15.02 Mean score: 34 → 59.6
IQ-Total	Mean score: 80.25 SD: ± 12.17 Action range: 64 → 106	Mean score: 84.39 SD: ± 12.13 Action range: 77 → 113	Mean score: 83.11 SD: ± 14.22 Action range: 74.5 → 124	Mean score: 88.33 SD: ± 28.30 Action range: 73 → 111
Education	Mean score: 9.67 SD: ± 2.78 5 years: 2.70% 8 years: 64.86% 13 years: 29.74% 18 years: 2.70%	Mean score: 10.83 SD: ± 2.93 5 years: 1.06% 8 years: 45.74% 13 years: 47.86% 18 years 5.31%	Mean score: 11.46 SD: ± 2.79 5 years 0% 8 years 35.20% 13 years 59.25% 18 years 5.55%	Mean score: 11.57 SD: ± 3.63 5 years 0% 8 years 42.86% 13 years 42.86% 18 years 14.28%
Correct Sequences (WM)	Mean score: 14.70 SD: ± 4.93 Action range: 12 → 24	Mean score: 16.49 SD: ± 4.78 Action range: 14 → 27	Mean scores: 17.48 SD: ± 5.23 Action range: 14 → 26	Mean score: 18.11 SD: ± 3.83 Action range: 13.5 → 21.5
Age	Mean score: 33.81 SD: ± 7.41 Action range: 21 → 55	Mean score: 23.15 SD: ± 5.19 Action range: 19.5 → 40	Mean score: 34.65 SD: ± 10.26 Action range: 19 → 32.5	Mean score: 35.12 SD: ± 8.35 Action range: 25.5 → 46.5
Tower of London (EF)	Mean score: 11.8 SD: ± 3.58 Action range: 9.25 → 21	Mean score: 12.75 SD: ± 4.32 Action range: 10 → 22	Mean score: 14.55 SD: ± 7.38 Action range: 8.8 → 19	Mean score: 15.09 SD: ± 3.83 Action range: 15 → 22
Token (Motor Coordination 30")	Mean score: 34.64 SD: ± 11.32 Action range: 24 → 59	Mean score: 33.94 SD: ± 9.82 Action range: 26 → 58	Mean score: 36.66 SD: ± 10.55 Action range: 30 → 50	Mean score: 35.87 SD: ± 8.46 Action range: 26 → 43
Perseverative Errors - WCST (EF)	Mean score: 21.69 SD: ± 14.45 Action range: 11.07 → 54.55	Mean score: 17.30 SD: ± 11.69 Action range: 7.81 → 46.88	Mean score: 13.96 SD: ± 9.77 Action range: 6.1 → 25.64	Mean score: 12.66 SD: ± 9.03 Action range 5.99 → 23.92
Sequence Length (WM)	Mean score: 5.71 SD: ± 1.56 Action range: 5 → 8	Mean score: 6.33 SD: ± 2.34 Action range: 5 → 24	Mean score: 6.50 SD: ± 2.52 Action range: 3 → 8	Mean score: 6.75 SD: ± 0.93 Action range: 6 → 8
PANSS-Negative	Mean score: 25.34 SD: ± 8.14 Action range: 21 → 40	Mean score: 21.27 SD ± 6.83 Action range: 16 → 38	Mean score: 17.27 SD: ± 7.03 Action range: 8.8 → 25.1	Mean score: 12.83 SD: ± 5.58 Action range: 6.75 → 19.8
Token (Motor Coordination 60")	Mean score: 67.46 SD: ± 22.52 Action range: 54 → 100	Mean score: 66.17 SD: ± 18.42 Action range: 52 → 100	Mean score: 72.37 SD: ± 16.59 Action range: 50 → 95	Mean score: 73.25 SD: ± 13.42 Action range: 60 → 88
Antipsychotic Therapy	1: Risperidone 15.79% 2: Haloperidol 5.26% 3: Clozapine 68.42% 4: Thioridazine 0% 5: Olanzapine 10.53% 6: Aripiprazole 0%	1: Risperidone 35.71% 2: Haloperidol 10.71% 3: Clozapine 42.86% 4: Thioridazine 0% 5: Olanzapine 8.93% 6: Aripiprazole 1.79%	1: Risperidone 30.43% 2: Haloperidol 26.09% 3: Clozapine 39.13% 4: Thioridazine 0% 5: Olanzapine 4.35% 6: Aripiprazole 0%	1: Risperidone 33.33% 2: Haloperidol 0% 3: Clozapine 66.67% 4: Thioridazine 0% 5: Olanzapine 0% 6: Aripiprazole 0%
Phonological Fluency	Mean score: 8.77 SD: ± 4.43 Action range: 6.75 → 20.5	Mean score: 9.45 SD: ± 3.87 Action range: 7 → 21.5	Mean score: 10.96 SD: ± 5.41 Action range: 5 → 14.25	Mean score: 11.9 SD: ± 4.77 Action range: 6.5 → 18.4
IQ-Verbal	Mean score: 84.68 SD: ± 13.42 Action range: 63 → 106	Mean score: 87.72 DS: ± 12.36 Action range: 78.5 → 114	Mean score: 87.28 SD: ± 14.85 Action range: 71.7 → 102	Mean score: 93 SD: ± 26 Action range: 79 → 123
IQ-Performance	Mean score: 77.43 SD: ± 12.62 Action range: 59 → 105	Mean score: 82.14 SD: ± 13.43 Action range: 74 → 116	Mean score: 81.55 SD: ± 15.47 Action range: 68 → 102	Mean score: 81 SD: ± 27.2 Action range: 70 → 103

PANSS: Positive and Negative Syndrome Scale; IQ: Intelligence Quotient; WM: Working Memory; EF: Executive Functions; WCST: Wisconsin Card Sorting Test; CPT: Continuous Performance Test.

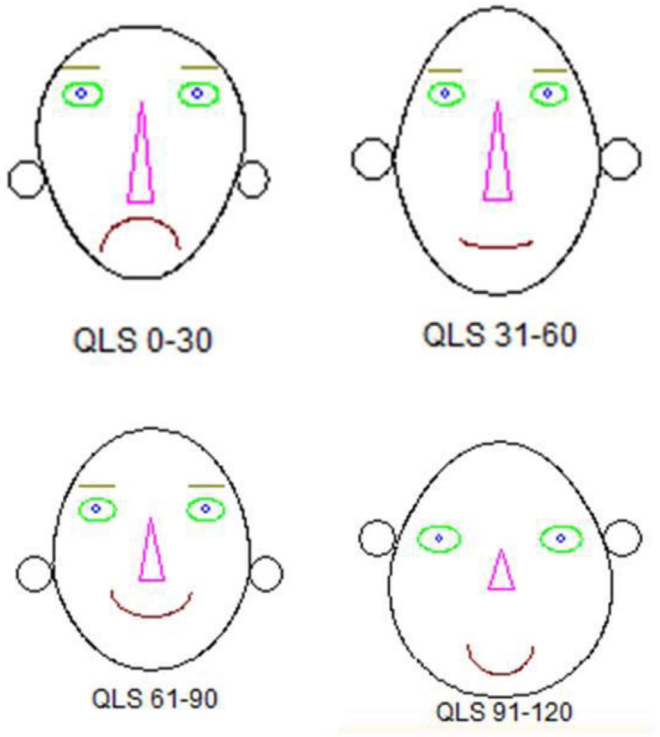

Fig. 1. Chernoff Faces summarizing our results concerning Profiles 1–4. Figure legend: Width of the Faces: Symbol Coding Score; Ears' Position: Missed Targets Forehead (length): List Learning Score from the Brief Assessment of Cognition in Schizophrenia; Forehead (Width): HITS on the Continuous Performance Test; Chin (Width): Semantic Fluency Score from the Brief Assessment of Cognition in Schizophrenia; Nose (Length): Positive and Negative Syndrome Scale Total Score; Mouth (Position): Total IQ; Mouth (Smile): Education.

represent vectorial transformations of the mean values of each significant predictor of functional outcome, with the exception of categorical variables, which were not taken into account for this analysis.

4. Discussion

The present study aimed to better analyze the relationships between psychopathological, neurocognitive and clinical variables with respect to their impact on daily functioning among patients with schizophrenia. Its primary goal was to construct several Profiles which would describe typical patterns of interaction among variables and capture clinical heterogeneity. Our results stress the composite nature of functional outcome. In fact, each patient may exhibit a unique medley of cognitive strengths and weaknesses, linked to a specific level of global functioning, due to the interplay among multiple variables (Bechi et al., 2017).

Currently, most available studies focus separately only single domains, such as neuropsychological or clinical variables (Buonocore et al., 2013) and apply linear statistical approaches. Such approaches are centered on the concepts of mean and standard deviation, with consequent difficulties in capturing heterogeneity. Given this background, the ANN approach was specifically chosen in order to overcome these methodological biases. In fact, one of ANNs main advantages is the simultaneous evaluation of the non-linear interactions among multiple, as well as the assessment of their importance (i.e. their weight) in predicting a target phenomenon (Basheer and Hajmeer, 2000). Moreover, ANNs allow to extract crucial descriptors for the determination of a specific output (i.e. functional outcome) by a multiplicity of computational tools, such as Sensitivity Analysis (Szaleniec, 2012). Finally, it is important to note that the present study included a comprehensive assessment of the main socio-demographic, clinical, psychopathological and neurocognitive variables. In particular, the neuropsychological tests were chosen among the most commonly used measures to assess cognitive domains which are known to be impaired in schizophrenia (Bechi et al., 2018).

Overall, results showed that all neurocognitive variables, as well as several clinical-demographic variables, play significant roles in functional outcome, as expected (Green and Harvey, 2014; Keefe et al., 2016).

With respect to the clinical and demographic data collected, the results highlighted the significant influence of negative symptoms, age and education level. These findings are in line with previous research stressing the association between functional capacity, demographic (e.g. education level) (Bechi et al., 2017) and clinical variables (e.g. symptomatology) (Mantovani et al., 2015). Interestingly, positive symptomatology was not suggested to be a key predictor of functional outcome. This supports the more prominent role of negative symptomatology (De Peri et al., 2013), especially among clinically stabilized patients with schizophrenia. Furthermore, based on its strong relationship to IQ, educational level might be considered as an indicator of premorbid functioning, which in turn might play a role in determining functional outcome (Bechi et al., 2017).

Focusing on neurocognition, which is the main predictor of functional outcome, interesting results emerged. Processing speed (i.e. Symbol Coding performance) turned out to be the first-ranked predictor of functional outcome. This is consistent with previous studies (Stern et al., 2005), suggesting a correlation between symbol coding task performance and patients' global disability level. Furthermore, processing speed was hypothesized to constitute the core deficit, as well as a proper endophenotype, of schizophrenia (Stern et al., 2005). More specifically, our findings are in line with those of Andersen and colleagues (Andersen et al., 2013) and suggest that processing speed might represent a crucial variable, with other variables depending on it (i.e. "speed-dependent variables" as encoding and retrieval processes, decision-making and perception). In other words, processing speed may be considered a factor underpinning higher-level neuropsychological deficits in schizophrenia (Ojeda et al., 2012; Rodriguez-Sanchez et al., 2007). Therefore, processing speed should be a primary focus of investigation when evaluating global functioning among patients with schizophrenia. This issue is also supported by a recent study, which suggested that visual attention and processing speed deficits might help to discriminate between remitted and non-remitted patients (Kurebayashi and Otaki, 2016). Secondly, attention measures and verbal memory were shown to have a major impact on functioning, in line with previous research (Dickinson et al., 2007; Fujii and Wylie, 2003). Thirdly, the role of other cognitive functions, including core domains of planning, cognitive flexibility and working memory, although significant, seems to be minor. This partially contradicts previous literature (Eisenberg and Berman, 2010) and may be explained by the different statistical methodologies or relies on individual variability. Furthermore, it should be noted that executive measures are influenced by other cognitive processes (i.e. task impurity problem).Finally, working memory constitutes a crucial element in the schizophrenia construct (Goldman-Rakic, 1994), but it is possible that the importance of its influence decreases when taking into account multiple variables at the same time.

The architecture of the self-organizing Profiles from Kohonen networks strongly relied on different levels of functioning. Each Profile presented both quantitative and qualitative differences with respect to others. On one hand, as expected, some key variables tended to show a "gradient pattern" among Profiles, so that individuals with better functional outcome tended, overall, to have better test performance and to show fewer symptoms. On the other hand, it is interesting to note that this tendency was not confirmed for all variables such as Hits and Missed Targets on the CPT, or the IQ measures which showed an irregular pattern among Profiles. Three out of four Profiles included outlier

subjects, which self-organized into defined Sub-Profiles. Each Sub-Profile showed a homogeneous pattern to its primary Profile in key predictive variables, while it exhibited similarity in lesser contributing variables to another primary Profile. Results thus strongly point out the heterogeneity underpinning clinical and outcome manifestations among patients with schizophrenia.

The study shows potential application for both clinical and research settings. As far as the theoretical perspectives are concerned, our findings might contribute to a better understanding of the links between neurocognition, clinical status and functional outcome, as well as to the identification of possible subtypes or endophenotypes of the disorder. In fact, by further elucidating the heterogeneity in both symptomatology and cognitive status, this approach may lead to the identification of subgroups of patients that may also display similar neurobiological alterations, providing a suitable model for the Research Domain Criteria (R-DoC) approach (Cuthbert, 2015). As far as the clinical implications are concerned, our Profiles might lead to the implemention of more individual-centered rehabilitative treatments. Such interventions should target the specific contributing factors and should be modulated on the basis of the individual's belonging type. More specifically, a sequential methodology addressing minor level components before addressing higher-level domains may provide more significant changes in functioning.

Indeed, this work has some limitations which must be considered. The presence of outlier subjects among three of four Profiles might suggest that extent of heterogeneity was not completely captured by the Profiles. Another key limitation is the exclusion of the social cognition domain from the assessment. Indeed social cognition has been recognized as one of the crucial features underling functional impairment in schizophrenia (Couture et al., 2006) and would mediate an indirect relationship between neuropsychological status and functional outcome (Roncone et al., 2013; Schmidt et al., 2011). It is important to consider that this is a pilot study and the inclusion of social cognitive variables would have led to an excessive methodological complexity also considering the sample size. Future research will be necessary to further investigate the role (and the weight) of social cognitive variables in determining functional outcome.

In conclusion, this study stresses the necessity of a more in-depth analysis of clinical and especially cognitive heterogeneity. For this purpose, integrating neuropsychological, clinical and psychopathological data by means of non-linear statistical approaches might help to better identify the building blocks of individual functioning. This might consequently pave the way to further implement tailored and personalized rehabilitation treatments in clinical practice.

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Declarations of interest

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Authors' contributions

Authors MBo, MBe and FB drafted the manuscript.

Authors MBe, MBo, MBu and RC designed the study and wrote the protocol.

Authors MBe, MBo, MBu, MS, FC, LB and CG contributed to the clinical study.

Author EP undertook the statistical analysis.

Authors FB and MS managed the literature searches and analyses.

All Authors contributed to data interpretation.

All Authors critically revised the manuscript.

All Authors contributed to and approved the final manuscript.

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