European Neuropsychopharmacology

Identifying pathways between psychiatric symptoms and psychosocial functioning in the general sample

--Manuscript Draft--

Manuscript Number:	ENP-22-78R3
Article Type:	Research article
Keywords:	psychiatric symptoms, functioning, web survey, network analysis, machine learning.
Corresponding Author:	Silvia Amoretti, Ph.D. SPAIN
First Author:	Francisco Diego Rabelo-da-Ponte, BSc, MSc
Order of Authors:	Francisco Diego Rabelo-da-Ponte, BSc, MSc
	Norma Verdolini, MD, PhD
	Jeferson Ferraz Goularte, PhD
	Silvia Dubou Serafim, BSc, MSc
	Marco Antonio Caldieraro, MD, PhD
	Eduard Vieta, MD, PhD
	J. Antoni Ramos-Quiroga, PhD
	Silvia Amoretti, PhD
	Adriane Ribeiro Rosa, PhD
Abstract:	The present study aims to identify pathways between psychiatric network symptoms and psychosocial functioning and their associated variables among functioning clusters in the general population. A cross-sectional web-based survey was administered in a total of 3,023 individuals in Brazil. The functioning clusters were derived by a previous study identifying three different groups based on the online Functioning Assessment Short Test. Networking analysis was fitted with all items of the Patient-Reported Outcomes Measurement Information System for depression and for anxiety (PROMIS) using the mixed graphical model. A decision tree model was used to identify the demographic and clinical characteristics of good and low functioning. A total of 926 (30.63%) subjects showed good functioning, 1,436 (47.50%) participants intermediate functioning, and 661 (21.86%) individuals low functioning. Anxiety and uneasy symptoms were the most important nodes for good and intermediate clusters but anxiety, feeling of failure, and depression were the most relevant symptoms for low functioning. The decision tree model was applied to identify variables capable to discriminate individuals with good and low functioning. The algorithm achieved balanced accuracy 0.75, sensitivity 0.87, specificity 0.63, positive predictive value 0.63 negative predictive value 0.87 (p<0.001), and an area under the curve of 0.83 (95%CI:0.79–0.86, p<0.01). Our results show that individuals who present psychological distress are more likely to experience poor functional status, suggesting that this subgroup should receive a more comprehensive psychiatric assessment and mental health care.

Ms. Ref. No.: ENP-22-78-R2

Title: Identifying pathways between psychiatric symptoms and psychosocial functioning in the general sample

European Neuropsychopharmacology

Dear Jose Sanchez-Moreno,

Please find enclosed our last revised version, which we produced after taking into account the suggestion by Reviewer 4. We used the track changes in Word document to facilitate comparison with the previous version. We hope that this version will meet the requirements for publication in European Neuropsychopharmacology,

Best regards,

Silvia Amoretti and Adriane Ribeiro Rosa

Highlights

- In the networking analysis, the most important nodes for good and intermediate functioning clusters were anxiety and uneasy symptoms. The relevant nodes for low functioning cluster were anxiety, feeling of failure, and depression.
- Our machine learning-based decision tree showed the low functioning cluster split into two parts: 1) subjects with symptoms of severe mental illness plus low income; 2) individuals with symptoms of severe mental illness plus age (<46 years old) plus middle income.
- The majority of good functioning cluster did not have any psychiatric symptoms

Reviewer 4: The manuscript is improved with this last change. However, the term "i a non-clinical population" should be replaced by the term "in the general population" because around 10% of the sample did include individials with psychiatric disorders (i.e., clinical populations).

Answer: Thank you for your comment. We have replaced "non-clinical population" by the term "general population".

Highlights

Highlights

- In the networking analysis, the most important nodes for good and intermediate functioning clusters were anxiety and uneasy symptoms. The relevant nodes for low functioning cluster were anxiety, feeling of failure, and depression.
- Our machine learning-based decision tree showed the low functioning cluster split into two parts: 1) subjects with symptoms of severe mental illness plus low income; 2) individuals with symptoms of severe mental illness plus age (<46 years old) plus middle income.
- The majority of good functioning cluster did not have any psychiatric symptoms .

Identifying pathways between psychiatric symptoms and psychosocial functioning in the general sample

Francisco Diego Rabelo-da-Ponte[1,‡], Norma Verdolini[2,‡], Jeferson Ferraz Goularte[3,4], Silvia Dubou Serafim[3,4], Marco Antonio Caldieraro[3,4], Eduard Vieta[5], J. Antoni Ramos-Quiroga [6,7,8,9], Silvia Amoretti [5,7 *], Adriane R Rosa[3,4,8*]

1. Department of Social, Genetic & Developmental Psychiatry, Institute of Psychology, Psychiatry and Neurosciences, King's College London, London, United Kingdom.
2. Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Biomedical Network Research Centre on Mental Health (CIBERSAM), 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.
3. Laboratory of Molecular Psychiatry, Centro de Pesquisa Experimental (CPE) and Centro de Pesquisa Clínica (CPC), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil. Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Porto Alegre, RS, Brazil.
4. Universidade Federal do Rio Grande do Sul, School of Medicine, Graduate Program in Psychiatry and Behavioral Sciences, Department of Psychiatry, Porto Alegre, RS, Brazil.
5. Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Biomedical Network Research Centre on Mental Health (CIBERSAM), 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.
6. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; Department of Psychiatry and Forensic Medicine, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain
7. Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autonoma de Barcelona, CIBERSAM, Barcelona, Catalonia, Spain
8. Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

‡ The first two authors contributed equally to this work.

*Corresponding authors: Silvia Amoretti, PhD. Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autonoma de Barcelona, CIBERSAM, Barcelona, Catalonia, Spain, Tel.: +34 93 489 38 80; fax: +34 93 489 45 87, Paseo Vall d'Hebron, 119-129, 08035 Barcelona (Spain). E-mail address: silvia.amoretti@vhir.org. Adriane Ribeiro Rosa, PhD. Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS). Avenida Ipiranga, 2752 Porto Alegre, RS 90.610-000 Brasil. Phone: +55 51 3308-5090 Fax: +55 51 3308-5437. E-mail address: adrianerrosa@gmail.com

Abstract

The present study aims to identify pathways between psychiatric network symptoms and psychosocial functioning and their associated variables among functioning clusters in the general population. A cross-sectional web-based survey was administered in a total of 3,023 individuals in Brazil. The functioning clusters were derived by a previous study identifying three different groups based on the online Functioning Assessment Short Test. Networking analysis was fitted with all items of the Patient-Reported Outcomes Measurement Information System for depression and for anxiety (PROMIS) using the mixed graphical model. A decision tree model was used to identify the demographic and clinical characteristics of good and low functioning. A total of 926 (30.63%) subjects showed good functioning, 1,436 (47.50%) participants intermediate functioning, and 661 (21.86%) individuals low functioning. Anxiety and uneasy symptoms were the most important nodes for good and intermediate clusters but anxiety, feeling of failure, and depression were the most relevant symptoms for low functioning. The decision tree model was applied to identify variables capable to discriminate individuals with good and low functioning. The algorithm achieved balanced accuracy 0.75, sensitivity 0.87, specificity 0.63, positive predictive value 0.63 negative predictive value 0.87 ($p<0.001$), and an area under the curve of 0.83 (95%CI:0.79–0.86, $p<0.01$). Our results show that individuals who present psychological distress are more likely to experience poor functional status, suggesting that this subgroup should receive a more comprehensive psychiatric assessment and mental health care.

Keywords: psychiatric symptoms, functioning, web survey, network analysis, machine learning.

1. Introduction

Depressive and anxious symptoms can commonly co-occur in a more severe psychopathological clinical presentation (Hirschfeld, 2001; Schoevers et al., 2005), associated with chronically persisting diminished health status and quality of life (Sherbourne et al., 1996). Particularly, they have been seen to be commonly associated with severe limitations in daily life (De Silva et al., 2013), both in psychiatric patients and in those suffering from a medical condition (Bishop et al., 2019; Shen et al., 2019). There is a possible overlap between depressive and anxiety disorders, probably relying on shared brain mechanisms and genes, as highlighted by shared treatment effects (Goodwin, 2015). In a study assessing the symptoms' structure of major depression, an agitation factor characterized by anxiety, helplessness, guilt, and irritability was found together with a general depressive symptom factor (Bares et al., 2011; Li et al., 2014). Nonetheless, another factor analysis examining the structure of anxiety and depression symptoms among adolescents revealed that two separated factors, one for depression and the other one for anxiety, were identified, underlying that even though the constructs of anxiety and depression have similar emotional features, they actually represent separate entities (Bares et al., 2011).

Furthermore, a systematic review of factor analyses in subjects with MDD showed two main dimensions of depressive symptoms: depressed mood and interest loss (van Loo et al., 2022, 2012) while Han-Chinese women with MDD identified a general depressive symptom factor and a guilt/suicidality factor as the two important dimensions (Li et al., 2014). More recently, it has been shown that cognitive and attitudinal changes such as worthlessness, hopelessness, and anxiety (identified as part of the cognitive affective dimensions) were the most important aspects to be considered to screen psychiatric conditions in general populations while sleep, appetite, and weight problems were strongly associated with age and body mass index (van Loo et al., 2022). These findings suggest the nature of symptom dimension may reflect a different structure and meaning, when evaluated in a clinical sample or in the general population. Additionally, another interesting aspect is to evaluate the clinical relevance of the symptom dimensions in terms of outcome, i.e. to examine the association between distinct dimension and psychosocial functioning.

Symptoms of depression and anxiety can often be accompanied by functional impairment (Malhi and Mann, 2018). One of the reasons for this is that there is a direct relationship between the number and severity of symptoms and an increased probability of functional impairment (Malhi and Mann, 2018). The development of evidence-based interventions focused on psychosocial functioning improvement has been suggested as a key for clinical recovery and the return of individuals to a previous performance at home, work, and/or school (Kamenov et al., 2017). Nevertheless, it is crucial to understand how depressive and anxious symptoms interacts among subjects with different levels of psychosocial impairment. In the light of these ideas, network analysis is an integrative approach to understanding psychopathological symptoms, as mental disorders can occur due to feedback loops between symptoms (Borsboom and Cramer, 2013). Thus, it is possible to build a mathematical model capable of mimicking the dynamics of symptoms (Borsboom and Cramer, 2013). From the network perspective, recognizing strong and weak links in a symptom network can provide a clinical opportunity to treat a person focused on their strong nodes, breaking the network and preventing a new mood episode for example (Borsboom and Cramer, 2013). A recent network analysis study found that anxiety symptoms have a high network centrality and a strong association with mood symptoms among individuals with major depression (Feiten et al., 2021). In particular, psychomotor symptoms (such as impaired motor skills, restlessness and inability to relax) presented a high bridge betweenness among the disorders (Wang et al., 2020).

Considering that depressive and anxious symptoms have also been consistently associated with functional impairment in psychiatric patients (Batterham et al., 2021; Zakeri et al., 2021), we aimed to identify pathways between psychiatric symptoms and psychosocial functioning in the general population. For that aim, we analyzed the network structure of the anxious and depressive symptoms' presentation of those participants with low versus intermediate versus those with a good psychosocial functioning. Finally, we developed a decision tree model to identify the clinical characteristics of good and low functioning.

2. Material and Methods

2.1 Participants

We administered a cross-sectional web-based survey using an anonymous online questionnaire available via social networks (Facebook, Instagram, WhatsApp, and Twitter) through shares, likes and comments without using paid traffic, that is, we used a convenience sampling strategy to target the adult Brazilian population. A total of 4,460 subjects started the questionnaire (response rate: 67.78%). The data were collected between May 20th and September 13th in 2020 in Brazil. The online questionnaire consisted of sociodemographic items (gender, age, income, education level), compliance to social distancing measures, assessment of previous psychiatric disorders, psychosocial functioning, and the severity of depression and anxiety. Online informed consent was obtained from the participants. The study was approved by the local ethics committee. All data was kept confidential in a password-protected computer. There was neither financial compensation for participation nor any penalty for not participating.

2.2 Assessments

2.2.1 Psychosocial functioning

The Functioning Assessment Short Test (FAST) was used to assess multiple areas of functioning, namely, autonomy, work, cognition, finance, interpersonal relationships and leisure (Rosa et al., 2007). Items in each domain were rated on a four-point scale, ranging from 0 (no difficulty) to 3 (severe difficulty), based on the two weeks prior to survey participation. The total score is the sum of each item (24 in total), and a higher score indicates worse functioning. The FAST is a transdiagnostic scale, validated in distinct clinical samples and available in several languages. Both the clinician- and the self-administrated versions have been validated (Bonnín et al., 2018; Cacilhas et al., 2009; Rosa et al., 2007). For the purposes of the present study, we used the online self-reported FAST scale that has been validated in a sample of Brazilian population, presenting a satisfactory psychometric property (Serafim et. al. 2022).

2.2.2 Psychiatric assessment

The severity of psychiatric symptoms was measured as follows:

I. The Patient-Reported Outcomes Measurement Information System (PROMIS) for depression (PROMIS Short Form v1.0 - Depression 8a) assesses negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).

II. The PROMIS Anxiety Short Form assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). Each of the PROMIS tools used consists of an 8-item questionnaire that assesses symptoms over the previous seven days, with items rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; 5=always). In the PROMIS depression questionnaire, the respondents were presented with the following statements: "In the past 7 days...1) *I felt worthless*; 2) *I felt helpless*; 3) *I felt depressed*; 4) *I felt hopeless*; 5) *I felt like a failure*; 6) *I felt unhappy*; 7) *I felt that I had nothing to look forward*;

8) *I felt that nothing could cheer me up*". In the PROMIS anxiety questionnaire, the respondents were presented with the following statements: "In the past 7 days...1) *I felt fearful*; 2) *I found it hard to focus on anything other than my anxiety*; 3) *My worries overwhelmed me*; 4) *I felt uneasy*; 5) *I felt nervous*; 6) *I felt like I needed help for my anxiety*; 7) *I felt anxious*; 8) *I felt tense*". All PROMIS scores are presented as T-scores calculated by the Health Measures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice) from the raw sum score, using T-scores from the general population of the United States. The T-score is a standardized score, with a mean of 50 and a standard deviation of 10. For depression and anxiety, a T-score lower or equal to 55 indicates no significant symptoms, scores between 55 and 60 indicate mild symptoms, scores between 60 and 70 indicate moderate symptoms, and severe symptoms are identified if scores range between 70 and 83 for depression and between 70 to 81 for anxiety. For the purpose of our study, we classified both PROMIS depression and anxiety T-scores into two categories of severity: no significant/mild symptoms (normal/mild symptoms) and moderate/severe symptoms.

III. For a general assessment of mental health, we used the DSM-5 Self-Rated Level 1 Cross- Cutting Symptom Measure, which assesses 13 psychiatric domains (depression, anger, mania, anxiety, somatic symptoms, sleep problems, memory, repetitive thoughts and behaviors, dissociation, personality function, suicidal ideation, psychosis, and substance use) over the previous 2 weeks. This tool has been used as a screening tool to assess the dimensional nature of mental health issues. Respondents indicate how much (or how often) they have been bothered by each symptom in the prior two weeks using a five-point response scale (1: none - not at all; 2: slight - rare, less than a day or two; 3: mild - several days; 4: moderate - more than half the days; 5: severe - nearly every day). Each item is rated on a 5-point Likert scale (0= none or not at all; 1= slightly rare, less than a day or two; 2= mild or several days; 3= moderate or more than half the days; and 4= severe or nearly every day). A rating of mild (i.e, 2) or greater on any item within a domain, or in the case of substance use, suicidal ideation, and psychosis, a rating of slight (i.e. 1) or greater, indicates symptomatology in this domain requiring further assessment. An operational clinical definition of severe mental illness, which represented a proxy for a diagnosis posed on the basis of a psychiatric interview, was used in order to assess the relevance of severe mental illness in our models. According to the definition of severe mental illness, we aggregated the items depression, mania, and psychosis into a variable (yes or no). The participants who required further assessment in all the three symptoms based on DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure were classified as presenting symptoms of severe mental illness.

2.3 Statistical analysis

2.3.1 Cluster analysis

We converted all functioning domains into Z-score using the whole sample size. Afterwards, we performed the Partition Around Medoids (PAM) algorithm (Schubert and Rousseeuw, 2019) to identify functioning clusters of subjects (package "fpc", version 2.2-9). We applied the Gower's distance to calculate the dissimilarities between pairs of subjects. We determined the optimal number of clusters through Gap statistic method (package "factoextra", version 1.0.7). Then, we performed a discriminant function analysis (DFA) (package "MASS", version 7.3-51.6) to confirm the clusters retained, and to investigate the predictive power of the clustering of each individual's functioning domain to the functioning subgroup. The cluster analysis is useful to identify subgroups within a sample. The cluster algorithm is an unsupervised machine learning technique which gathers participants based on their similarities and split them according to their dissimilarities. Additionally, we applied the PAM algorithm instead of other clustering methods as it is one of the most robust techniques to deal with noise and outliers (Schubert and Rousseeuw, 2019). We used R software (version 4.0.2) and RStudio (version 3.5.3) for all analyses.

2.3.2 Networking analysis

After that, we performed the network analysis with all items of the PROMIS for depression and for anxiety applying Gaussian Markov random field estimation and graphical Least Absolute Shrinkage and Selection Operator (LASSO) regression with extended Bayesian information criterion to select optimal regularization parameter and avoid spurious connections among nodes through "bootnet" (version 1.4.3) and "qgraph" (version 1.9.2) packages (Costantini et al., 2015; Epskamp et al., 2018, 2012). The network structure has some centrality indices such as strength, closeness, and betweenness (Opsahl et al., 2010). We calculated the centrality indices through the package "qgraph" (version 1.6.5). The strength quantifies the direct connection of a node (symptom) to other ones, i.e., measures the importance of a node in the network. Closeness assesses how well a node is connecting to the other nodes indirectly. Betweenness measures the number of times the shortest path between two nodes passes through a given node, that is, betweenness indicates the importance of a node as a link among others (Opsahl et al., 2010). After that, we verified the stability of the centrality indices, we performed a case-dropping bootstrap network estimation method with 1,000 repetitions with correlation stability coefficient (CS-coefficient) (package “bootnet”, version 1.4.3). The CS-coefficient calculates a correlation between the original network and the network with less cases (Epskamp et al., 2018). This metric should not be below 0.25 and preferably above 0.5 (Epskamp et al., 2018). We performed three network comparison tests (package "NetworkComparisonTest", version 2.2.1) with 1,000 permutations and False Discovery Rate (FDR) as a post-hoc test for multiple comparison to estimate the difference between good functioning vs. intermediate functioning, good functioning vs. low functioning, and intermediate functioning vs. low functioning. The network comparison test is an advanced and useful methodology to assesses the difference between two networks by using several invariance metrics such as network structure invariance (networks are the same) and global strength invariance (the sum of all connection weights is equal)(Feiten et al., 2021; Isvoranu et al., 2022; van Borkulo et al., 2022).

2.3.3 Decision tree algorithm

We used Recursive Partitioning and Regression Trees (RPART) algorithm (package “rpart”, version 4.1.15; “rpart.plot”, version, 3.1.1) to identify the clinical characteristics of subjects with good and low functioning in the general population (Strobl et al., 2009). That algorithm is a machine learning method that considers all predictors but it automatically selects the best variable to discriminate the group. Besides that, RPART shows the importance of variables graphically, in which the variables on top are the most relevant to classify the groups with their respective cut-offs (Rhys, 2020). The beginning of the tree is called the root and then, at each branch, the algorithm chooses the best variable to discriminate a group. That technique is useful to identify complex nonlinear relations between variables and outcomes (Lantz, 2013). For this reason, RPART algorithm has some advantages: 1) automatically selects important variables and determines cut-offs according to data; 2) handles both categorical and continuous variables; 3) produces an output that it is easy to understand because it is a white box model (Rabelo-da-Ponte et al., 2020).

We included just the good and low functioning clusters into the decision tree model because they are the most contrasting groups and because the algorithm performs better using dichotomous outcomes rather than multiclass outcomes. We inserted the following variables in the model: gender (male or female), income (in Brazilian real-BRL,high, BRL >10,386.52; middle, BRL >2,965.69-10,386.52; or low income, BRL <708.19-2,965.69), symptoms of severe mental illness (yes or no), educational level (less than high school/postsecondary non-tertiary education or undergraduate/graduate level), and age. We included those variables because they are highly associated psychosocial functioning (Crossley et al., 2022; Dalsgaard et al., 2020a, 2020b; Frey et al., 2020). Among subjects with good and low functioning, we split our dataset into training (70%) and test the dataset (30%) randomly ("caret", version 6.0-91). After that, we used a standard machine-learning protocol with 10-fold cross-validation to evaluate the model's performance. Then, we tested the decision tree model in the test dataset and the model performance was calculated based on balanced accuracy, sensitivity, specificity, the positive predictive value, the negative predictive value, and the area under the receiver operating characteristic (ROC) curve (AUC) (package "pROC", version 1.18). It is important to highlight that we deleted missing data since all algorithms do not handle missing values.

3. Results

3.1 Networking analysis among three different functional clusters

A total of 3,023 individuals completed the survey. The sample was composed mostly by female gender (84,1%, n=2,543), and the mean age was 34,28 years (18-79). Most participants had low (35,5%, n=1,074) or middle (46,1%, n=1,395) income, and higher educational level (57%, n=1,723). Most subjects had no symptoms of severe mental illness (90,5%, n=2,736). Among the total sample, 926 (30.63%) subjects showed good functioning, 1,436 (47.50%) were classified as intermediate functioning, and 661 (21.86%) were participants with low functioning. The symptom networks among the functioning clusters displayed different patterns (Fig. 1) and networks achieved a good stability (Supplementary figure 1). In the good functioning cluster, the CS-coefficient achieved 0.55, 0.59, and 0.69 of betweenness, closeness, and strength, respectively. In relation to the intermediate cluster, this metric had 0.58, 0.61, and 0.75 of betweenness, closeness, and strength, respectively. The CS-coefficient values for betweenness, closeness, and strength were 0.36, 0.33, and 0.69, respectively, in the low functioning cluster.

In relation to the network comparison test, the global strength between good functioning (7.54) and intermediate functioning (7.51) showed no difference between them (0.03, $p=0.81$) and no statistical difference for network structure invariance (0.12, $p=0.19$). In the second comparison, there was no difference in global connectivity (0.28, $p=0.07$) between intermediate functioning (7.51) and low functioning (7.22) nor in network structure invariance (0.1, $p=0.63$). However, there was a statistical difference in global strength (0.32, $p<0.05$) between good functioning and low functioning. The network structure invariance is the same among them (0.14, $p=0.2$).

Anxiety and uneasy symptoms were the first and second most central nodes in the strength measurements in the good and intermediate functioning clusters. In these clusters, uneasy feeling and depressive mood presented the highest connection weight in terms of betweenness and closeness. In the low functioning cluster, anxiety was also the most central node, followed by feelings of failure, while the connection with the highest weight was between depressed mood and anxiety (Fig. 2).

3.2Decision tree algorithm

The decision tree model achieved balanced accuracy 0.75, sensitivity 0.87, specificity 0.63, positive predictive value 0.63, and negative predictive value 0.87 ($p<0.001$). Furthermore, the model had an AUC of 0.83 (10-fold cross-validation; 95% CI 0.79–0.86, $p<0.01$) (Supplementary figure 2). Among all variables inserted in the model, educational status and gender were not selected by the decision tree algorithm (Fig. 3). The split criterion is indicated in each decision node. The most important variable was having symptoms of severe mental illness, which split the root node into two branches (no symptoms of severe mental illness for the good functioning subgroup and with severe mental illness for the low functioning cluster). The second most relevant variable was economic status followed by age and economic status again. Having symptoms of severe mental illness and low income classified a portion of individuals with low functioning cluster (30%) as long as severe mental illness, age less than 46 years-old and middle income classified another portion of individuals with low functioning (26%). Thus, these results revealed that at least 76% of the patients with symptoms of severe mental illness showed low functioning.

Nevertheless, individuals with good functioning had three different splits. One of them, they were participants without symptoms of severe mental illness (27%). Another portion had symptoms of severe mental illness, high/middle income and were older (≥ 46 years of age) (9%) but the last portion of the same cluster were younger (< 46 years of age) and high income (6%).

4. Discussion

In the present study, we estimated three networks of anxiety and depression symptoms from three functioning clusters (good, intermediate and low functioning) in the general population. Additionally, we used a machine learning-based decision tree algorithm to identify variables related to good and low functioning. Our major findings were: 1. Individuals with good psychosocial functioning displayed anxiety and distress symptoms as central nodes whilst individuals presenting worst psychosocial functioning presented anxiety and feeling of failure as the most relevant nodes of their psychopathological condition; 2. Specific characteristics were associated with the low functioning cluster; having symptoms of severe mental illness and low income whilst another portion of individuals were younger than 46 years old and had middle income. Accordingly, the most important variable that differentiated individuals with good or low psychosocial functioning was having symptoms of severe mental illness. The second most relevant variable was economic status followed by age. Finally, younger individuals with lower income presented lower psychosocial functioning.

As for the association between psychopathological symptoms and psychosocial functioning, it is well-known that both anxious and depressive symptoms affect psychosocial functioning. In the present study, those individuals that presented low psychosocial functioning reported anxiety and feeling of failure that resulted to be the most relevant nodes of the specific network analysis. Accordingly, a previous study identified that 85% of patients suffering from major depressive disorders (MDD) reported feelings of inadequacy and self-blaming emotions as the most bothersome symptoms (Zahn et al., 2015). Interestingly, a research identified that self-blame was the depressive symptom most associated with difficulties in close relationships, the domain of psychosocial functioning identifying impairment in interpersonal relationships (Fried and Nesse, 2014). Network analysis allows gaining insights into the complex nature of co-occurring symptoms and symptom dimensions, and mainly identifying core symptoms. In the present study, we identified that the connections between and among symptoms differ depending on the psychosocial functioning of the individuals. As a consequence, the present findings can be used to guide the clinical evaluation and possible interventions based on the identification of core symptoms of anxiety and depression and functioning clusters. Mainly, these findings pointed at the importance of providing Psychiatry care at people presenting anxiety and depressive feelings, particularly feelings of failure, in order to improve their psychosocial functioning, which is, together with symptom severity, one of the most important aspect in psychiatry, allowing better quality of life and functional lives for people suffering from psychiatric conditions.

Noteworthy, the decision tree model identified that low functioning was associated with having symptoms of a severe mental illness (such as symptoms of bipolar disorder, MDD and psychosis). Among psychiatric disorders, the first cause of disease burden is depression, followed by schizophrenia as the third cause and BD is the 5th leading cause (Vigo et al., 2016). Among mental and neurological disorders, the highest amount of DALYs is attributable to MDD whilst schizophrenia and BD are the 7th and 8th causes, respectively (Catalá-López et al., 2013).

Furthermore, the decision tree model reported that low functioning was associated with younger age and low income. As for the association between age and functioning, previous literature assessing functional outcomes in different study populations identified that younger age was generally characterized by worse psychosocial functioning (Moser et al., 2013; Rapoport and Feinstein, 2001). Similarly, younger age was strongly associated with higher severity of psychiatric symptoms such as depression, anxiety, and stress in the Brazilian population (Goularte et al., 2021). In another study, significant improvements in social functioning and general mental health were identified with increasing age (Hemingway et al., 1997). Even with mental disorder and being younger (<46 years old), having middle income had association with low functioning, compared to those with high income who had good functioning.

Finally, income was an important variable associated with poor psychosocial functioning since work ability tends to decrease after 46 years of age. However, not all individuals are affected to the same extent, and those with low-income families, that unfortunately represent a huge part of population in developing countries like Brazil, were specially affected and those should be protected from the effects of socioeconomic adversities (Rocha et al., 2021). Our results are in line with previous studies that have shown the impact of socioeconomic status on cognitive functioning and psychological well-being, in particular, in those individuals with certain degree of psychopathology (Czepielewski et al., 2022).

The interpretation of the results of the present study should be taken in light of the following limitations. First, we used an online survey with a convenience sample method that may not be a representative sample of the total Brazilian general population. Second, all outcomes were self- reported instead of evaluated by a clinician. Third, this study was conducted during the COVID-19 pandemic, which may have some influence on result interpretations. Fourth this is a cross-sectional study and did not provide causal evidence of risk factors and mental health outcomes found in our study. Finally, psychiatric symptoms and functional status were self- reported assessment instead of evaluated by a clinician. Since it is an online cross-sectional study, we cannot provide a diagnosis based on a psychiatric evaluation and we could not assess the diagnoses longitudinally. It is for this reason that in our study we used an operational clinical definition of severe mental illness, which represented a proxy for a diagnosis based on a psychiatric interview. Although this does not represent a formal psychiatric diagnosis, it suggests a certain degree of psychological distress. Through the identification of psychiatric diagnoses proxies that allowed a screening of the mental health status of the general population, we would like to point out that a poor psychosocial functioning was associated with psychological distress in the general population and psychiatric help should be provided to the general population, to those who were younger and with a lower income.

In conclusion, this study identifies pathways between psychopathology and functional impairment and is the first to conduct an assessment of anxious and depressive symptoms and their network structure in relation with distinct levels of the specific grade of psychosocial functioning among a consistent sample of the Brazilian general population. Furthermore, it provides useful indications to the governments on which are those factors that should be addressed in order to reduce functional impairment, specifically socio-economic issues and mental health.

Reference

Bares, C.B., Andrade, F., Delva, J., Grogan-Kaylor, A., 2011. Examining the Factor Structure of Anxiety and Depression Symptom Items Among Adolescents in Santiago, Chile. J. Soc. Social Work Res. 2. https://doi.org/10.5243/jsswr.2011.1

Batterham, P.J., Calear, A.L., McCallum, S.M., Morse, A.R., Banfield, M., Farrer, L.M., Gulliver, A., Cherbuin, N., Rodney Harris, R.M., Shou, Y., Dawel, A., 2021. Trajectories of depression and anxiety symptoms during the COVID-19 pandemic in a representative Australian adult cohort. Med. J. Aust. 214, 462–468.

Bishop, C., Mulraney, M., Rinehart, N., Sciberras, E., 2019. An examination of the association between anxiety and social functioning in youth with ADHD: A systematic review. Psychiatry Res. 273, 402–421.

Bonnín, C.M., Martínez-Arán, A., Reinares, M., Valentí, M., Solé, B., Jiménez, E., Montejo, L., Vieta, E., Rosa, A.R., 2018. Thresholds for severity, remission and recovery using the functioning assessment short test (FAST) in bipolar disorder. J. Affect. Disord. 240, 57–62.

Borsboom, D., Cramer, A.O.J., 2013. Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 9, 91–121.

Cacilhas, A.A., Magalhães, P.V. da S., Ceresér, K.M., Walz, J.C., Weyne, F., Rosa, A.R., Vieta, E., Kapczinski, F., 2009. Validity of a short functioning test (FAST) in Brazilian outpatients with bipolar disorder. Value Health 12, 624–627.

Catalá-López, F., Gènova-Maleras, R., Vieta, E., Tabarés-Seisdedos, R., 2013. The increasing burden of mental and neurological disorders. Eur. Neuropsychopharmacol. 23, 1337–1339.

Costantini, G., Epskamp, S., Borsboom, D., Perugini, M., Mõttus, R., Waldorp, L.J., Cramer, A.O.J., 2015. State of the aRt personality research: A tutorial on network analysis of personality data in R. J. Res. Pers. 54, 13–29.

Crossley, N.A., Alliende, L.M., Czepielewski, L.S., Aceituno, D., Castañeda, C.P., Diaz, C., Iruretagoyena, B., Mena, C., Mena, C., Ramirez-Mahaluf, J.P., Tepper, A., Vasquez, J., Fonseca, L., Machado, V., Hernández, C.E., Vargas-Upegui, C., Gomez-Cruz, G., Kobayashi-Romero, L.F., Moncada-Habib, T., Arango, C., Barch, D.M., Carter, C., Correll, C.U., Freimer, N.B., McGuire, P., Evans-Lacko, S., Undurraga, E., Bressan, R., Gama, C.S., Lopez-Jaramillo, C., de la Fuente-Sandoval, C., Gonzalez-Valderrama, A., Undurraga, J., Gadelha, A., 2022. The enduring gap in educational attainment in schizophrenia according to the past 50 years of published research: a systematic review and meta-analysis. Lancet Psychiatry 9, 565–573.

Czepielewski, L.S., Alliende, L.M., Castañeda, C.P., Castro, M., Guinjoan, S.M., Massuda, R., Berberian, A.A., Fonseca, A.O., Gadelha, A., Bressan, R., Crivelaro, M., Louzã, M., Undurraga, J., González-Valderrama, A., Nachar, R., Nieto, R.R., Montes, C., Silva, H., Langer, Á.I., Schmidt, C., Mayol-Troncoso, R., Díaz-Zuluaga, A.M., Valencia-Echeverry, J., López-Jaramillo, C., Solís-Vivanco, R., Reyes-Madrigal, F., de la Fuente-Sandoval, C., Crossley, N.A., Gama, C.S., ANDES Network, 2022. Effects of Socioeconomic Status in Cognition of People with Schizophrenia: Results From a Latin American Collaboration Network with 1175 Subjects - Corrigendum. Psychol. Med. 1.

Dalsgaard, S., McGrath, J., Østergaard, S.D., Wray, N.R., Pedersen, C.B., Mortensen, P.B., Petersen, L., 2020a. Association of Mental Disorder in Childhood and Adolescence With Subsequent Educational Achievement. JAMA Psychiatry 77, 797–805.

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B.B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K.B., Timmerman, A., Schendel, D., McGrath, J.J., Mortensen, P.B., Pedersen, C.B., 2020b. Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. JAMA Psychiatry 77, 155–164.

De Silva, M.J., Cooper, S., Li, H.L., Lund, C., Patel, V., 2013. Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. Br. J. Psychiatry 202, 253–260.

Epskamp, S., Borsboom, D., Fried, E.I., 2018. Estimating psychological networks and their accuracy: A tutorial paper. Behav. Res. Methods 50, 195–212.
Epskamp, S., Cramer, A.O.J., Waldorp, L.J., Schmittmann, V.D., Borsboom, D., 2012. qgraph: Network Visualizations of Relationships in Psychometric Data. J. Stat. Softw. 48. https://doi.org/10.18637/jss.v048.i04
Feiten, J.G., Mosqueiro, B.P., Uequed, M., Passos, I.C., Fleck, M.P., Caldieraro, M.A., 2021. Evaluation of major depression symptom networks using clinician-rated and patient-rated data. J. Affect. Disord. 292, 583–591.
Frey, B.N., Vigod, S., de Azevedo Cardoso, T., Librenza-Garcia, D., Favotto, L., Perez, R., Kapczinski, F., 2020. The Early Burden of Disability in Individuals With Mood and Other Common Mental Disorders in Ontario, Canada. JAMA Netw Open 3, e2020213.
Fried, E.I., Nesse, R.M., 2014. The impact of individual depressive symptoms on impairment of psychosocial functioning. PLoS One 9, e90311.
Goodwin, G.M., 2015. The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues Clin. Neurosci. 17, 249–260.
Goularte, J.F., Serafim, S.D., Colombo, R., Hogg, B., Caldieraro, M.A., Rosa, A.R., 2021. COVID-19 and mental health in Brazil: Psychiatric symptoms in the general population. J. Psychiatr. Res. 132, 32–37.
Hemingway, H., Nicholson, A., Stafford, M., Roberts, R., Marmot, M., 1997. The impact of socioeconomic status on health functioning as assessed by the SF-36 questionnaire: the Whitehall II Study. Am. J. Public Health 87, 1484–1490.
Hirschfeld, R.M.A., 2001. The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim. Care Companion J. Clin. Psychiatry 3, 244–254.
Isvoranu, A.-M., Epskamp, S., Waldorp, L., Borsboom, D., 2022. Network Psychometrics with R: A Guide for Behavioral and Social Scientists. Routledge.
Kamenov, K., Twomey, C., Cabello, M., Prina, A.M., Ayuso-Mateos, J.L., 2017. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol. Med. 47, 1337.
Lantz, B., 2013. Machine Learning with R. Packt Publishing Ltd.
Li, Y., Aggen, S., Shi, S., Gao, J., Li, Y., Tao, M., Zhang, K., Wang, X., Gao, C., Yang, L., Liu, Y., Li, K., Shi, J., Wang, G., Liu, L., Zhang, J., Du, B., Jiang, G., Shen, J., Zhang, Z., Liang, W., Sun, J., Hu, J., Liu, T., Wang, X., Miao, G., Meng, H., Li, Y., Hu, C., Li, Y., Huang, G., Li, G., Ha, B., Deng, H., Mei, Q., Zhong, H., Gao, S., Sang, H., Zhang, Y., Fang, X., Yu, F., Yang, D., Liu, T., Chen, Y., Hong, X., Wu, W., Chen, G., Cai, M., Song, Y., Pan, J., Dong, J., Pan, R., Zhang, W., Shen, Z., Liu, Z., Gu, D., Wang, X., Liu, X., Zhang, Q., Flint, J., Kendler, K.S., 2014. The structure of the symptoms of major depression: exploratory and confirmatory factor analysis in depressed Han Chinese women. Psychol. Med. 44, 1391–1401.
Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312.
Moser, D.K., Heo, S., Lee, K.S., Hammash, M., Riegel, B., Lennie, T.A., Arslanian-Engoren, C., Mudd-Martin, G., Albert, N., Watkins, J., 2013. "It could be worse ... lot"s worse!' Why health-related quality of life is better in older compared with younger individuals with heart failure. Age Ageing 42, 626–632.
Opsahl, T., Agneessens, F., Skvoretz, J., 2010. Node centrality in weighted networks: Generalizing degree and shortest paths. Social Networks. https://doi.org/10.1016/j.socnet.2010.03.006
Rabelo-da-Ponte, F.D., Lima, F.M., Martinez-Aran, A., Kapczinski, F., Vieta, E., Rosa, A.R., Kunz, M., Czepielewski, L.S., 2020. Data-driven cognitive phenotypes in subjects with bipolar disorder and their clinical markers of severity. Psychol. Med. 1–8.
Rapoport, M.J., Feinstein, A., 2001. Age and functioning after mild traumatic brain injury: the acute picture. Brain Inj. 15, 857–864.
Rhys, H., 2020. Machine Learning with R, the tidyverse, and mlr. Simon and Schuster.
Rocha, R., Atun, R., Massuda, A., Rache, B., Spinola, P., Nunes, L., Lago, M., Castro, M.C., 2021. Effect of socioeconomic inequalities and vulnerabilities on health-system preparedness and response to COVID-19 in Brazil:

a comprehensive analysis. Lancet Glob. Health 9, e782–e792.
Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Ment. Health 3, 5.
Schoevers, R.A., Deeg, D.J.H., van Tilburg, W., Beekman, A.T.F., 2005. Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. Am. J. Geriatr. Psychiatry 13, 31–39.
Schubert, E., Rousseeuw, P.J., 2019. Faster k-Medoids Clustering: Improving the PAM, CLARA, and CLARANS Algorithms. Similarity Search and Applications. https://doi.org/10.1007/978-3-030-32047-8_16
Shen, B.-J., Fan, Y., Lim, K.S.C., Tay, H.Y., 2019. Depression, Anxiety, Perceived Stress, and Their Changes Predict Greater Decline in Physical Health Functioning over 12 Months Among Patients with Coronary Heart Disease. Int. J. Behav. Med. 26, 352–364.
Sherbourne, C.D., Wells, K.B., Meredith, L.S., Jackson, C.A., Camp, P., 1996. Comorbid anxiety disorder and the functioning and well-being of chronically ill patients of general medical providers. Arch. Gen. Psychiatry 53, 889–895.
Serafim, S.D., Goularte, J.F., Caldieraro, M.A., Lima, F. M., Dalpiaz, G., Rabelo-da-Ponte, F.D., Torrent C., Solé, B., Vieta, E., Rosa, A.R.. Validity and reliability of the Digital Functioning Assessment Short Test (D-FAST) in Brazilian sample. *Clinical Practice and Epidemiology in Mental Health* 18, 2022.
Strobl, C., Malley, J., Tutz, G., 2009. An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. Psychol. Methods 14, 323–348.
van Borkulo, C.D., van Bork, R., Boschloo, L., Kossakowski, J.J., Tio, P., Schoevers, R.A., Borsboom, D., Waldorp, L.J., 2022. Comparing network structures on three aspects: A permutation test. Psychol. Methods. https://doi.org/10.1037/met0000476
van Loo, H.M., Aggen, S.H., Kendler, K.S., 2022. The structure of the symptoms of major depression: Factor analysis of a lifetime worst episode of depressive symptoms in a large general population sample. J. Affect. Disord. 307, 115–124.
van Loo, H.M., de Jonge, P., Romeijn, J.-W., Kessler, R.C., Schoevers, R.A., 2012. Data-driven subtypes of major depressive disorder: a systematic review. BMC Med. 10, 156.
Vigo, D., Thornicroft, G., Atun, R., 2016. Estimating the true global burden of mental illness. Lancet Psychiatry 3, 171–178.
Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C.S., Ho, R.C., 2020. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int. J. Environ. Res. Public Health 17. https://doi.org/10.3390/ijerph17051729
Zahn, R., Lythe, K.E., Gethin, J.A., Green, S., Deakin, J.F.W., Young, A.H., Moll, J., 2015. The role of self-blame and worthlessness in the psychopathology of major depressive disorder. J. Affect. Disord. 186, 337–341.
Zakeri, M.A., Hossini Rafsanjanipoor, S.M., Kahnooji, M., Ghaedi Heidari, F., Dehghan, M., 2021. Generalized Anxiety Disorder During the COVID-19 Outbreak in Iran: The Role of Social Dysfunction. J. Nerv. Ment. Dis. 209, 491–496.

Figure 1

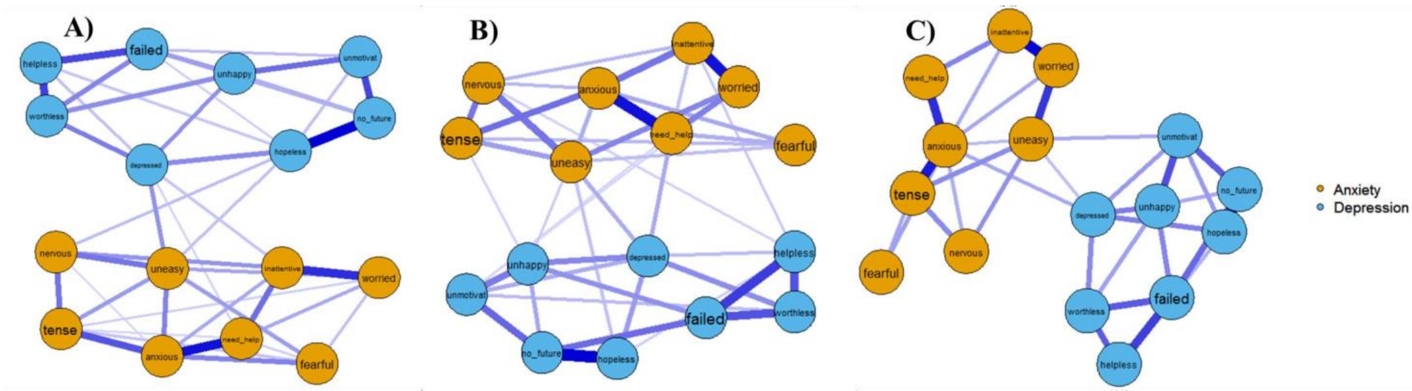

Figure 1. Networks of symptoms among three functioning clusters. A) Network of symptoms for subjects with good functioning. B) Network of symptoms for participants with intermediate functioning. C) Network of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. Different color nodes represent different PROMIS domains. Blue lines indicate a positive association between two symptoms. Thicker edges represent stronger associations and thinner edges mean weaker association. The meaning of acronyms for depressive symptoms: *worthless* — *I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful

— *I felt fearful*; innatentive — *I found it hard to focus on anything other than my anxiety*; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*".

Figure 2
2.docx

Click here to access/download;Figure(s);Figure

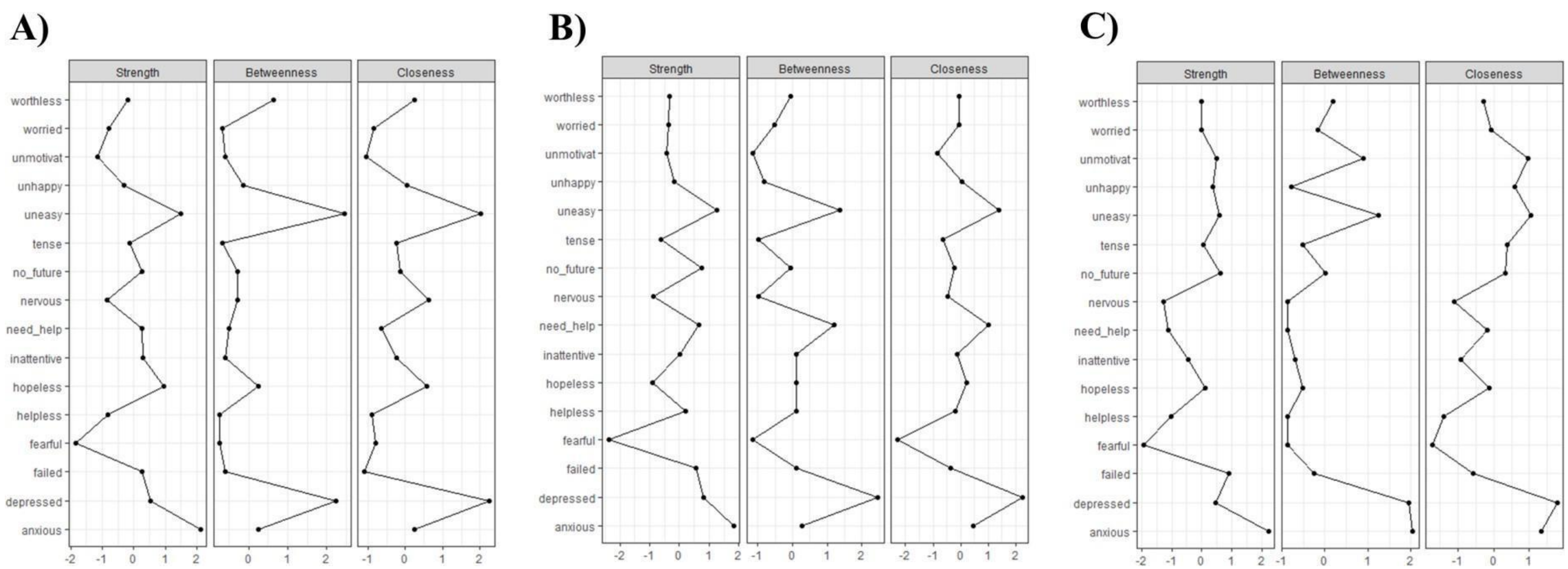

Figure 2. Centrality measures among three functioning clusters. A) Centrality measures of symptoms for subjects with good functioning. B) Centrality measures of symptoms for participants with intermediate functioning. C) Centrality measures of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. The meaning of acronyms for depressive symptoms: *worthless* — *I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful — *I felt fearful*; innatentive — *I*

found it hard to focus on anything other than my anxiety; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*”.

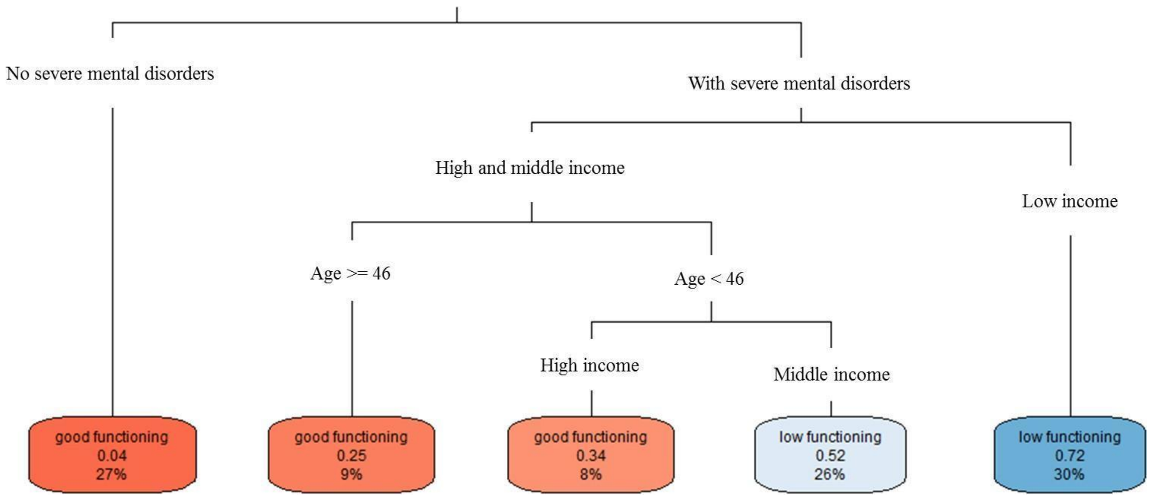

Figure 3. Decision tree using RPART algorithm to identify the clinical characteristics of subjects with good and low functioning in the general population. Each node shows three information: 1) the predicted class (good or low functioning); 2) the predicted probability of the predicted class; 3) the percentage of observation at the node in relation to the entire sample size.

Fundings

"This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) –Finance Code 001".
“This work received financial supports from Conselho Nacional de Desenvolvimento
304 Científico e Tecnológico

Author's contribution

Conceptualization: FDRP, ARR, NV, SA. Data Curation: FDRP, ARR, FRG, SDS, SA.

Formal Analysis: FDRP, ARR, NV, SA. Investigation: FDRP, ARR, FRG, SDS, SA, MAC, EV, JARQ.

Methodology: FDRP, ARR, FRG, SDS, SA, MAC.

Project Administration: ARR, FRG, SDS, MAC.

Supervision: ARR, SA, EV, JARQ, MAC.

Validation: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS.

Visualization: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS, ED, JARQ.

Writing – Original Draft Preparation: FDRP, NV, SA. Writing –

Review&Editing: SA, ARR, ED, MAC, JARQ.

Conflict of Interest

Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

Josep Antoni Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen- Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli-Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

Norma Verdolini has received financial support for CME activities and travel funds from the following entities (unrelated to the present work): Angelini, Janssen, Lundbeck, Otsuka.

Marco Antonio Caldieraro has received grants from the following entities (unrelated to the present work): Conselho Nacional de Desenvolvimento Científico e Tecnológico, and Janssen.

The rest of authors report no biomedical financial interests or potential conflicts of interest related to the present article.

Acknowledgment

We are extremely grateful to all the participants.

Eduard Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283, PI18/00805) integrated into the Plan Nacional de I + D + I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365) and the CERCA Programme / Generalitat de Catalunya. He would like to thank the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357.

Silvia Amoretti has been supported by a Sara Borrell contract (CD20/00177), funded by Instituto de Salud Carlos III (ISCIII) and co-funded by European Social Fund "Investing in your future".

Adriane R Rosa thanks to the CNPq process 302382/2019-4. Jéferson F Goularte thanks to 300 Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES).

Supplementary Material 1

Click here to access/download
Supplementary Material
suplementary_figure1.docx

Highlights

- In the networking analysis, the most important nodes for good and intermediate functioning clusters were anxiety and uneasy symptoms. The relevant nodes for low functioning cluster were anxiety, feeling of failure, and depression.
- Our machine learning-based decision tree showed the low functioning cluster split into two parts: 1) subjects with symptoms of severe mental illness plus low income; 2) individuals with symptoms of severe mental illness plus age (<46 years old) plus middle income.
- The majority of good functioning cluster did not have any psychiatric symptoms .

Identifying pathways between psychiatric symptoms and psychosocial functioning in ~~a non-clinical~~the general sample

Francisco Diego Rabelo-da-Ponte[1,‡], Norma Verdolini[2,‡], Jeferson Ferraz Goularte[3,4], Silvia Dubou Serafim[3,4], Marco Antonio Caldieraro[3,4], Eduard Vieta[5], J. Antoni Ramos-Quiroga [6,7,8,9], Silvia Amoretti [5,7 *], Adriane R Rosa[3,4,8*]

1. Department of Social, Genetic & Developmental Psychiatry, Institute of Psychology, Psychiatry and Neurosciences, King's College London, London, United Kingdom.
2. Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Biomedical Network Research Centre on Mental Health (CIBERSAM), 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.
3. Laboratory of Molecular Psychiatry, Centro de Pesquisa Experimental (CPE) and Centro de Pesquisa Clínica (CPC), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil. Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Porto Alegre, RS, Brazil.
4. Universidade Federal do Rio Grande do Sul, School of Medicine, Graduate Program in Psychiatry and Behavioral Sciences, Department of Psychiatry, Porto Alegre, RS, Brazil.
5. Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Biomedical Network Research Centre on Mental Health (CIBERSAM), 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.
6. Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; Department of Psychiatry and Forensic Medicine, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain
7. Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autonoma de Barcelona, CIBERSAM, Barcelona, Catalonia, Spain
8. Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

‡ The first two authors contributed equally to this work.

*Corresponding authors: Silvia Amoretti, PhD. Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Universitat Autonoma de Barcelona, CIBERSAM, Barcelona, Catalonia, Spain, Tel.: +34 93 489 38 80; fax: +34 93 489 45 87, Paseo Vall d'Hebron, 119-129, 08035 Barcelona (Spain). E-mail address: silvia.amoretti@vhir.org. Adriane Ribeiro Rosa, PhD. Department of Pharmacology, Federal University of Rio Grande do Sul (UFRGS). Avenida Ipiranga, 2752 Porto Alegre, RS 90.610-000 Brasil. Phone: +55 51 3308-5090 Fax: +55 51 3308-5437. E-mail address: adrianerrosa@gmail.com

Abstract

The present study aims to identify pathways between psychiatric network symptoms and psychosocial functioning and their associated variables among functioning clusters in the general population. A cross-sectional web-based survey was administered in a total of 3,023 individuals in Brazil. The functioning clusters were derived by a previous study identifying three different groups based on the online Functioning Assessment Short Test. Networking analysis was fitted with all items of the Patient-Reported Outcomes Measurement Information System for depression and for anxiety (PROMIS) using the mixed graphical model. A decision tree model was used to identify the demographic and clinical characteristics of good and low functioning. A total of 926 (30.63%) subjects showed good functioning, 1,436 (47.50%) participants intermediate functioning, and 661 (21.86%) individuals low functioning. Anxiety and uneasy symptoms were the most important nodes for good and intermediate clusters but anxiety, feeling of failure, and depression were the most relevant symptoms for low functioning. The decision tree model was applied to identify variables capable to discriminate individuals with good and low functioning. The algorithm achieved balanced accuracy 0.75, sensitivity 0.87, specificity 0.63, positive predictive value 0.63 negative predictive value 0.87 ($p<0.001$), and an area under the curve of 0.83 (95%CI:0.79–0.86, $p<0.01$). Our results show that individuals who present psychological distress are more likely to experience poor functional status, suggesting that this subgroup should receive a more comprehensive psychiatric assessment and mental health care.

Keywords: psychiatric symptoms, functioning, web survey, network analysis, machine learning.

1. Introduction

Depressive and anxious symptoms can commonly co-occur in a more severe psychopathological clinical presentation (Hirschfeld, 2001; Schoevers et al., 2005), associated with chronically persisting diminished health status and quality of life (Sherbourne et al., 1996). Particularly, they have been seen to be commonly associated with severe limitations in daily life (De Silva et al., 2013), both in psychiatric patients and in those suffering from a medical condition (Bishop et al., 2019; Shen et al., 2019). There is a possible overlap between depressive and anxiety disorders, probably relying on shared brain mechanisms and genes, as highlighted by shared treatment effects (Goodwin, 2015). In a study assessing the symptoms' structure of major depression, an agitation factor characterized by anxiety, helplessness, guilt, and irritability was found together with a general depressive symptom factor (Bares et al., 2011; Li et al., 2014). Nonetheless, another factor analysis examining the structure of anxiety and depression symptoms among adolescents revealed that two separated factors, one for depression and the other one for anxiety, were identified, underlying that even though the constructs of anxiety and depression have similar emotional features, they actually represent separate entities (Bares et al., 2011).

Furthermore, a systematic review of factor analyses in subjects with MDD showed two main dimensions of depressive symptoms: depressed mood and interest loss (van Loo et al., 2022, 2012) while Han-Chinese women with MDD identified a general depressive symptom factor and a guilt/suicidality factor as the two important dimensions (Li et al., 2014). More recently, it has been shown that cognitive and attitudinal changes such as worthlessness, hopelessness, and anxiety (identified as part of the cognitive affective dimensions) were the most important aspects to be considered to screen psychiatric conditions in general populations while sleep, appetite, and weight problems were strongly associated with age and body mass index (van Loo et al., 2022). These findings suggest the nature of symptom dimension may reflect a different structure and meaning, when evaluated in a clinical sample or in the general population. Additionally, another interesting aspect is to evaluate the clinical relevance of the symptom dimensions in terms of outcome, i.e. to examine the association between distinct dimension and psychosocial functioning.

Symptoms of depression and anxiety can often be accompanied by functional impairment (Malhi and Mann, 2018). One of the reasons for this is that there is a direct relationship between the number and severity of symptoms and an increased probability of functional impairment (Malhi and Mann, 2018). The development of evidence-based interventions focused on psychosocial functioning improvement has been suggested as a key for clinical recovery and the return of individuals to a previous performance at home, work, and/or school (Kamenov et al., 2017). Nevertheless, it is crucial to understand how depressive and anxious symptoms interacts among subjects with different levels of psychosocial impairment. In the light of these ideas, network analysis is an integrative approach to understanding psychopathological symptoms, as mental disorders can occur due to feedback loops between symptoms (Borsboom and Cramer, 2013). Thus, it is possible to build a mathematical model capable of mimicking the dynamics of symptoms (Borsboom and Cramer, 2013). From the network perspective, recognizing strong and weak links in a symptom network can provide a clinical opportunity to treat a person focused on their strong nodes, breaking the network and preventing a new mood episode for example (Borsboom and Cramer, 2013). A recent network analysis study found that anxiety symptoms have a high network centrality and a strong association with mood symptoms among individuals with major depression (Feiten et al., 2021). In particular, psychomotor symptoms (such as impaired motor skills, restlessness and inability to relax) presented a high bridge betweenness among the disorders (Wang et al., 2020).

Considering that depressive and anxious symptoms have also been consistently associated with functional impairment in psychiatric patients (Batterham et al., 2021; Zakeri et al., 2021), we aimed to identify pathways between psychiatric symptoms and psychosocial functioning in ~~non-clinical sample~~the general population. For that aim, we analyzed the network structure of the anxious and depressive symptoms' presentation of those participants with low versus intermediate versus those with a good psychosocial functioning. Finally, we developed a decision tree model to identify the clinical characteristics of good and low functioning.

2. Material and Methods

2.1 Participants

We administered a cross-sectional web-based survey using an anonymous online questionnaire available via social networks (Facebook, Instagram, WhatsApp, and Twitter) through shares, likes and comments without using paid traffic, that is, we used a convenience sampling strategy to target the adult Brazilian population. A total of 4,460 subjects started the questionnaire (response rate: 67.78%). The data were collected between May 20th and September 13th in 2020 in Brazil. The online questionnaire consisted of sociodemographic items (gender, age, income, education level), compliance to social distancing measures, assessment of previous psychiatric disorders, psychosocial functioning, and the severity of depression and anxiety. Online informed consent was obtained from the participants. The study was approved by the local ethics committee. All data was kept confidential in a password-protected computer. There was neither financial compensation for participation nor any penalty for not participating.

2.2 Assessments

2.2.1 Psychosocial functioning

The Functioning Assessment Short Test (FAST) was used to assess multiple areas of functioning, namely, autonomy, work, cognition, finance, interpersonal relationships and leisure (Rosa et al., 2007). Items in each domain were rated on a four-point scale, ranging from 0 (no difficulty) to 3 (severe difficulty), based on the two weeks prior to survey participation. The total score is the sum of each item (24 in total), and a higher score indicates worse functioning. The FAST is a transdiagnostic scale, validated in distinct clinical samples and available in several languages. Both the clinician- and the self-administrated versions have been validated (Bonnín et al., 2018; Cacilhas et al., 2009; Rosa et al., 2007). For the purposes of the present study, we used the online self-reported FAST scale that has been validated in a sample of Brazilian population, presenting a satisfactory psychometric property (Serafim et. al. 2022).

2.2.2 Psychiatric assessment

The severity of psychiatric symptoms was measured as follows:

I. The Patient-Reported Outcomes Measurement Information System (PROMIS) for depression (PROMIS Short Form v1.0 - Depression 8a) assesses negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).

II. The PROMIS Anxiety Short Form assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). Each of the PROMIS tools used consists of an 8-item questionnaire that assesses symptoms over the previous seven days, with items rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; 5=always). In the PROMIS depression questionnaire, the respondents were presented with the following statements: “In the past 7 days...1) *I felt worthless*; 2) *I felt helpless*; 3) *I felt depressed*; 4) *I felt hopeless*; 5) *I felt like a failure*; 6) *I felt unhappy*; 7) *I felt that I had nothing to look forward*;

8) *I felt that nothing could cheer me up*". In the PROMIS anxiety questionnaire, the respondents were presented with the following statements: "In the past 7 days...1) *I felt fearful*; 2) *I found it hard to focus on anything other than my anxiety*; 3) *My worries overwhelmed me*; 4) *I felt uneasy*; 5) *I felt nervous*; 6) *I felt like I needed help for my anxiety*; 7) *I felt anxious*; 8) *I felt tense*". All PROMIS scores are presented as T-scores calculated by the Health Measures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice) from the raw sum score, using T-scores from the general population of the United States. The T-score is a standardized score, with a mean of 50 and a standard deviation of 10. For depression and anxiety, a T-score lower or equal to 55 indicates no significant symptoms, scores between 55 and 60 indicate mild symptoms, scores between 60 and 70 indicate moderate symptoms, and severe symptoms are identified if scores range between 70 and 83 for depression and between 70 to 81 for anxiety. For the purpose of our study, we classified both PROMIS depression and anxiety T-scores into two categories of severity: no significant/mild symptoms (normal/mild symptoms) and moderate/severe symptoms.

III. For a general assessment of mental health, we used the DSM-5 Self-Rated Level 1 Cross- Cutting Symptom Measure, which assesses 13 psychiatric domains (depression, anger, mania, anxiety, somatic symptoms, sleep problems, memory, repetitive thoughts and behaviors, dissociation, personality function, suicidal ideation, psychosis, and substance use) over the previous 2 weeks. This tool has been used as a screening tool to assess the dimensional nature of mental health issues. Respondents indicate how much (or how often) they have been bothered by each symptom in the prior two weeks using a five-point response scale (1: none - not at all; 2: slight - rare, less than a day or two; 3: mild - several days; 4: moderate - more than half the days; 5: severe - nearly every day). Each item is rated on a 5-point Likert scale (0= none or not at all; 1= slightly rare, less than a day or two; 2= mild or several days; 3= moderate or more than half the days; and 4= severe or nearly every day). A rating of mild (i.e, 2) or greater on any item within a domain, or in the case of substance use, suicidal ideation, and psychosis, a rating of slight (i.e. 1) or greater, indicates symptomatology in this domain requiring further assessment. An operational clinical definition of severe mental illness, which represented a proxy for a diagnosis posed on the basis of a psychiatric interview, was used in order to assess the relevance of severe mental illness in our models. According to the definition of severe mental illness, we aggregated the items depression, mania, and psychosis into a variable (yes or no). The participants who required further assessment in all the three symptoms based on DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure were classified as presenting symptoms of severe mental illness.

2.3 Statistical analysis

2.3.1 Cluster analysis

We converted all functioning domains into Z-score using the whole sample size. Afterwards, we performed the Partition Around Medoids (PAM) algorithm (Schubert and Rousseeuw, 2019) to identify functioning clusters of subjects (package "fpc", version 2.2-9). We applied the Gower's distance to calculate the dissimilarities between pairs of subjects. We determined the optimal number of clusters through Gap statistic method (package "factoextra", version 1.0.7). Then, we performed a discriminant function analysis (DFA) (package "MASS", version 7.3-51.6) to confirm the clusters retained, and to investigate the predictive power of the clustering of each individual's functioning domain to the functioning subgroup. The cluster analysis is useful to identify subgroups within a sample. The cluster algorithm is an unsupervised machine learning technique which gathers participants based on their similarities and split them according to their dissimilarities. Additionally, we applied the PAM algorithm instead of other clustering methods as it is one of the most robust techniques to deal with noise and outliers (Schubert and Rousseeuw, 2019). We used R software (version 4.0.2) and RStudio (version 3.5.3) for all analyses.

2.3.2 Networking analysis

After that, we performed the network analysis with all items of the PROMIS for depression and for anxiety applying Gaussian Markov random field estimation and graphical Least Absolute Shrinkage and Selection Operator (LASSO) regression with extended Bayesian information criterion to select optimal regularization parameter and avoid spurious connections among nodes through "bootnet" (version 1.4.3) and "qgraph" (version 1.9.2) packages (Costantini et al., 2015; Epskamp et al., 2018, 2012). The network structure has some centrality indices such as strength, closeness, and betweenness (Opsahl et al., 2010). We calculated the centrality indices through the package "qgraph" (version 1.6.5). The strength quantifies the direct connection of a node (symptom) to other ones, i.e., measures the importance of a node in the network. Closeness assesses how well a node is connecting to the other nodes indirectly. Betweenness measures the number of times the shortest path between two nodes passes through a given node, that is, betweenness indicates the importance of a node as a link among others (Opsahl et al., 2010). After that, we verified the stability of the centrality indices, we performed a case-dropping bootstrap network estimation method with 1,000 repetitions with correlation stability coefficient (CS-coefficient) (package “bootnet”, version 1.4.3). The CS-coefficient calculates a correlation between the original network and the network with less cases (Epskamp et al., 2018). This metric should not be below 0.25 and preferably above 0.5 (Epskamp et al., 2018). We performed three network comparison tests (package "NetworkComparisonTest", version 2.2.1) with 1,000 permutations and False Discovery Rate (FDR) as a post-hoc test for multiple comparison to estimate the difference between good functioning vs. intermediate functioning, good functioning vs. low functioning, and intermediate functioning vs. low functioning. The network comparison test is an advanced and useful methodology to assesses the difference between two networks by using several invariance metrics such as network structure invariance (networks are the same) and global strength invariance (the sum of all connection weights is equal)(Feiten et al., 2021; Isvoranu et al., 2022; van Borkulo et al., 2022).

2.3.3 Decision tree algorithm

We used Recursive Partitioning and Regression Trees (RPART) algorithm (package “rpart”, version 4.1.15; “rpart.plot”, version, 3.1.1) to identify the clinical characteristics of subjects with good and low functioning in ~~non-clinical sample~~the general population (Strobl et al., 2009). That algorithm is a machine learning method that considers all predictors but it automatically selects the best variable to discriminate the group. Besides that, RPART shows the importance of variables graphically, in which the variables on top are the most relevant to classify the groups with their respective cut-offs (Rhys, 2020). The beginning of the tree is called the root and then, at each branch, the algorithm chooses the best variable to discriminate a group. That technique is useful to identify complex nonlinear relations between variables and outcomes (Lantz, 2013). For this reason, RPART algorithm has some advantages: 1) automatically selects important variables and determines cut-offs according to data; 2) handles both categorical and continuous variables; 3) produces an output that it is easy to understand because it is a white box model (Rabelo-da-Ponte et al., 2020).

We included just the good and low functioning clusters into the decision tree model because they are the most contrasting groups and because the algorithm performs better using dichotomous outcomes rather than multiclass outcomes. We inserted the following variables in the model: gender (male or female), income (in Brazilian real-BRL,high, BRL >10,386.52; middle, BRL >2,965.69-10,386.52; or low income, BRL <708.19-2,965.69), symptoms of severe mental illness (yes or no), educational level (less than high school/postsecondary non-tertiary education or undergraduate/graduate level), and age. We included those variables because they are highly associated psychosocial functioning (Crossley et al., 2022; Dalsgaard et al., 2020a, 2020b; Frey et al., 2020). Among subjects with good and low functioning, we split our dataset into training (70%) and test the dataset (30%) randomly ("caret", version 6.0-91). After that, we used a standard machine-learning protocol with 10-fold cross-validation to evaluate the model's performance. Then, we tested the decision tree model in the test dataset and the model performance was calculated based on balanced accuracy, sensitivity, specificity, the positive predictive value, the negative predictive value, and the area under the receiver operating characteristic (ROC) curve (AUC) (package "pROC", version 1.18). It is important to highlight that we deleted missing data since all algorithms do not handle missing values.

3. Results

3.1 Networking analysis among three different functional clusters

A total of 3,023 individuals completed the survey. The sample was composed mostly by female gender (84,1%, n=2,543), and the mean age was 34,28 years (18-79). Most participants had low (35,5%, n=1,074) or middle (46,1%, n=1,395) income, and higher educational level (57%, n=1,723). Most subjects had no symptoms of severe mental illness (90,5%, n=2,736). Among the total sample, 926 (30.63%) subjects showed good functioning, 1,436 (47.50%) were classified as intermediate functioning, and 661 (21.86%) were participants with low functioning. The symptom networks among the functioning clusters displayed different patterns (Fig. 1) and networks achieved a good stability (Supplementary figure 1). In the good functioning cluster, the CS-coefficient achieved 0.55, 0.59, and 0.69 of betweenness, closeness, and strength, respectively. In relation to the intermediate cluster, this metric had 0.58, 0.61, and 0.75 of betweenness, closeness, and strength, respectively. The CS-coefficient values for betweenness, closeness, and strength were 0.36, 0.33, and 0.69, respectively, in the low functioning cluster.

In relation to the network comparison test, the global strength between good functioning (7.54) and intermediate functioning (7.51) showed no difference between them (0.03, $p=0.81$) and no statistical difference for network structure invariance (0.12, $p=0.19$). In the second comparison, there was no difference in global connectivity (0.28, $p=0.07$) between intermediate functioning (7.51) and low functioning (7.22) nor in network structure invariance (0.1, $p=0.63$). However, there was a statistical difference in global strength (0.32, $p<0.05$) between good functioning and low functioning. The network structure invariance is the same among them (0.14, $p=0.2$).

Anxiety and uneasy symptoms were the first and second most central nodes in the strength measurements in the good and intermediate functioning clusters. In these clusters, uneasy feeling and depressive mood presented the highest connection weight in terms of betweenness and closeness. In the low functioning cluster, anxiety was also the most central node, followed by feelings of failure, while the connection with the highest weight was between depressed mood and anxiety (Fig. 2).

3.2Decision tree algorithm

The decision tree model achieved balanced accuracy 0.75, sensitivity 0.87, specificity 0.63, positive predictive value 0.63, and negative predictive value 0.87 ($p<0.001$). Furthermore, the model had an AUC of 0.83 (10-fold cross-validation; 95% CI 0.79–0.86, $p<0.01$) (Supplementary figure 2). Among all variables inserted in the model, educational status and gender were not selected by the decision tree algorithm (Fig. 3). The split criterion is indicated in each decision node. The most important variable was having symptoms of severe mental illness, which split the root node into two branches (no symptoms of severe mental illness for the good functioning subgroup and with severe mental illness for the low functioning cluster). The second most relevant variable was economic status followed by age and economic status again. Having symptoms of severe mental illness and low income classified a portion of individuals with low functioning cluster (30%) as long as severe mental illness, age less than 46 years-old and middle income classified another portion of individuals with low functioning (26%). Thus, these results revealed that at least 76% of the patients with symptoms of severe mental illness showed low functioning.

Nevertheless, individuals with good functioning had three different splits. One of them, they were participants without symptoms of severe mental illness (27%). Another portion had symptoms of severe mental illness, high/middle income and were older (≥ 46 years of age) (9%) but the last portion of the same cluster were younger (< 46 years of age) and high income (6%).

4. Discussion

In the present study, we estimated three networks of anxiety and depression symptoms from three functioning clusters (good, intermediate and low functioning) in ~~non-clinical sample~~the general population. Additionally, we used a machine learning-based decision tree algorithm to identify variables related to good and low functioning. Our major findings were: 1. Individuals with good psychosocial functioning displayed anxiety and distress symptoms as central nodes whilst individuals presenting worst psychosocial functioning presented anxiety and feeling of failure as the most relevant nodes of their psychopathological condition; 2. Specific characteristics were associated with the low functioning cluster; having symptoms of severe mental illness and low income whilst another portion of individuals were younger than 46 years old and had middle income. Accordingly, the most important variable that differentiated individuals with good or low psychosocial functioning was having symptoms of severe mental illness. The second most relevant variable was economic status followed by age. Finally, younger individuals with lower income presented lower psychosocial functioning.

As for the association between psychopathological symptoms and psychosocial functioning, it is well-known that both anxious and depressive symptoms affect psychosocial functioning. In the present study, those individuals that presented low psychosocial functioning reported anxiety and feeling of failure that resulted to be the most relevant nodes of the specific network analysis. Accordingly, a previous study identified that 85% of patients suffering from major depressive disorders (MDD) reported feelings of inadequacy and self-blaming emotions as the most bothersome symptoms (Zahn et al., 2015). Interestingly, a research identified that self-blame was the depressive symptom most associated with difficulties in close relationships, the domain of psychosocial functioning identifying impairment in interpersonal relationships (Fried and Nesse, 2014). Network analysis allows gaining insights into the complex nature of co-occurring symptoms and symptom dimensions, and mainly identifying core symptoms. In the present study, we identified that the connections between and among symptoms differ depending on the psychosocial functioning of the individuals. As a consequence, the present findings can be used to guide the clinical evaluation and possible interventions based on the identification of core symptoms of anxiety and depression and functioning clusters. Mainly, these findings pointed at the importance of providing Psychiatry care at people presenting anxiety and depressive feelings, particularly feelings of failure, in order to improve their psychosocial functioning, which is, together with symptom severity, one of the most important aspect in psychiatry, allowing better quality of life and functional lives for people suffering from psychiatric conditions.

Noteworthy, the decision tree model identified that low functioning was associated with having symptoms of a severe mental illness (such as symptoms of bipolar disorder, MDD and psychosis). Among psychiatric disorders, the first cause of disease burden is depression, followed by schizophrenia as the third cause and BD is the 5th leading cause (Vigo et al., 2016). Among mental and neurological disorders, the highest amount of DALYs is attributable to MDD whilst schizophrenia and BD are the 7th and 8th causes, respectively (Catalá-López et al., 2013).

Furthermore, the decision tree model reported that low functioning was associated with younger age and low income. As for the association between age and functioning, previous literature assessing functional outcomes in different study populations identified that younger age was generally characterized by worse psychosocial functioning (Moser et al., 2013; Rapoport and Feinstein, 2001). Similarly, younger age was strongly associated with higher severity of psychiatric symptoms such as depression, anxiety, and stress in the Brazilian population (Goularte et al., 2021). In another study, significant improvements in social functioning and general mental health were identified with increasing age (Hemingway et al., 1997). Even with mental disorder and being younger (<46 years old), having middle income had association with low functioning, compared to those with high income who had good functioning.

Finally, income was an important variable associated with poor psychosocial functioning since work ability tends to decrease after 46 years of age. However, not all individuals are affected to the same extent, and those with low-income families, that unfortunately represent a huge part of population in developing countries like Brazil, were specially affected and those should be protected from the effects of socioeconomic adversities (Rocha et al., 2021). Our results are in line with previous studies that have shown the impact of socioeconomic status on cognitive functioning and psychological well-being, in particular, in those individuals with certain degree of psychopathology (Czepielewski et al., 2022).

The interpretation of the results of the present study should be taken in light of the following limitations. First, we used an online survey with a convenience sample method that may not be a representative sample of the total Brazilian general population. Second, all outcomes were self- reported instead of evaluated by a clinician. Third, this study was conducted during the COVID-19 pandemic, which may have some influence on result interpretations. Fourth this is a cross-sectional study and did not provide causal evidence of risk factors and mental health outcomes found in our study. Finally, psychiatric symptoms and functional status were self- reported assessment instead of evaluated by a clinician. Since it is an online cross-sectional study, we cannot provide a diagnosis based on a psychiatric evaluation and we could not assess the diagnoses longitudinally. It is for this reason that in our study we used an operational clinical definition of severe mental illness, which represented a proxy for a diagnosis based on a psychiatric interview. Although this does not represent a formal psychiatric diagnosis, it suggests a certain degree of psychological distress. Through the identification of psychiatric diagnoses proxies that allowed a screening of the mental health status of the general population, we would like to point out that a poor psychosocial functioning was associated with psychological distress in ~~non-clinical sample~~the general population and psychiatric help should be provided to the general population, to those who were younger and with a lower income.

In conclusion, this study identifies pathways between psychopathology and functional impairment and is the first to conduct an assessment of anxious and depressive symptoms and their network structure in relation with distinct levels of the specific grade of psychosocial functioning among a consistent sample of the Brazilian general population. Furthermore, it provides useful indications to the governments on which are those factors that should be addressed in order to reduce functional impairment, specifically socio-economic issues and mental health.

Reference

Bares, C.B., Andrade, F., Delva, J., Grogan-Kaylor, A., 2011. Examining the Factor Structure of Anxiety and Depression Symptom Items Among Adolescents in Santiago, Chile. J. Soc. Social Work Res. 2. https://doi.org/10.5243/jsswr.2011.1

Batterham, P.J., Calear, A.L., McCallum, S.M., Morse, A.R., Banfield, M., Farrer, L.M., Gulliver, A., Cherbuin, N., Rodney Harris, R.M., Shou, Y., Dawel, A., 2021. Trajectories of depression and anxiety symptoms during the COVID-19 pandemic in a representative Australian adult cohort. Med. J. Aust. 214, 462–468.

Bishop, C., Mulraney, M., Rinehart, N., Sciberras, E., 2019. An examination of the association between anxiety and social functioning in youth with ADHD: A systematic review. Psychiatry Res. 273, 402–421.

Bonnín, C.M., Martínez-Arán, A., Reinares, M., Valentí, M., Solé, B., Jiménez, E., Montejo, L., Vieta, E., Rosa, A.R., 2018. Thresholds for severity, remission and recovery using the functioning assessment short test (FAST) in bipolar disorder. J. Affect. Disord. 240, 57–62.

Borsboom, D., Cramer, A.O.J., 2013. Network analysis: an integrative approach to the structure of psychopathology. Annu. Rev. Clin. Psychol. 9, 91–121.

Cacilhas, A.A., Magalhães, P.V. da S., Cerésér, K.M., Walz, J.C., Weyne, F., Rosa, A.R., Vieta, E., Kapczinski, F., 2009. Validity of a short functioning test (FAST) in Brazilian outpatients with bipolar disorder. Value Health 12, 624–627.

Catalá-López, F., Gènova-Maleras, R., Vieta, E., Tabarés-Seisdedos, R., 2013. The increasing burden of mental and neurological disorders. Eur. Neuropsychopharmacol. 23, 1337–1339.

Costantini, G., Epskamp, S., Borsboom, D., Perugini, M., Mõttus, R., Waldorp, L.J., Cramer, A.O.J., 2015. State of the aRt personality research: A tutorial on network analysis of personality data in R. J. Res. Pers. 54, 13–29.

Crossley, N.A., Alliende, L.M., Czepielewski, L.S., Aceituno, D., Castañeda, C.P., Diaz, C., Iruretagoyena, B., Mena, C., Mena, C., Ramirez-Mahaluf, J.P., Tepper, A., Vasquez, J., Fonseca, L., Machado, V., Hernández, C.E., Vargas-Upegui, C., Gomez-Cruz, G., Kobayashi-Romero, L.F., Moncada-Habib, T., Arango, C., Barch, D.M., Carter, C., Correll, C.U., Freimer, N.B., McGuire, P., Evans-Lacko, S., Undurraga, E., Bressan, R., Gama, C.S., Lopez-Jaramillo, C., de la Fuente-Sandoval, C., Gonzalez-Valderrama, A., Undurraga, J., Gadelha, A., 2022. The enduring gap in educational attainment in schizophrenia according to the past 50 years of published research: a systematic review and meta-analysis. Lancet Psychiatry 9, 565–573.

Czepielewski, L.S., Alliende, L.M., Castañeda, C.P., Castro, M., Guinjoan, S.M., Massuda, R., Berberian, A.A., Fonseca, A.O., Gadelha, A., Bressan, R., Crivelaro, M., Louzã, M., Undurraga, J., González-Valderrama, A., Nachar, R., Nieto, R.R., Montes, C., Silva, H., Langer, Á.I., Schmidt, C., Mayol-Troncoso, R., Díaz-Zuluaga, A.M., Valencia-Echeverry, J., López-Jaramillo, C., Solís-Vivanco, R., Reyes-Madrigal, F., de la Fuente-Sandoval, C., Crossley, N.A., Gama, C.S., ANDES Network, 2022. Effects of Socioeconomic Status in Cognition of People with Schizophrenia: Results From a Latin American Collaboration Network with 1175 Subjects - Corrigendum. Psychol. Med. 1.

Dalsgaard, S., McGrath, J., Østergaard, S.D., Wray, N.R., Pedersen, C.B., Mortensen, P.B., Petersen, L., 2020a. Association of Mental Disorder in Childhood and Adolescence With Subsequent Educational Achievement. JAMA Psychiatry 77, 797–805.

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B.B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K.B., Timmerman, A., Schendel, D., McGrath, J.J., Mortensen, P.B., Pedersen, C.B., 2020b. Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. JAMA Psychiatry 77, 155–164.

De Silva, M.J., Cooper, S., Li, H.L., Lund, C., Patel, V., 2013. Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. Br. J. Psychiatry 202, 253–260.

Epskamp, S., Borsboom, D., Fried, E.I., 2018. Estimating psychological networks and their accuracy: A tutorial paper. Behav. Res. Methods 50, 195–212.
Epskamp, S., Cramer, A.O.J., Waldorp, L.J., Schmittmann, V.D., Borsboom, D., 2012. qgraph: Network Visualizations of Relationships in Psychometric Data. J. Stat. Softw. 48. https://doi.org/10.18637/jss.v048.i04
Feiten, J.G., Mosqueiro, B.P., Uequed, M., Passos, I.C., Fleck, M.P., Caldieraro, M.A., 2021. Evaluation of major depression symptom networks using clinician-rated and patient-rated data. J. Affect. Disord. 292, 583–591.
Frey, B.N., Vigod, S., de Azevedo Cardoso, T., Librenza-Garcia, D., Favotto, L., Perez, R., Kapczinski, F., 2020. The Early Burden of Disability in Individuals With Mood and Other Common Mental Disorders in Ontario, Canada. JAMA Netw Open 3, e2020213.
Fried, E.I., Nesse, R.M., 2014. The impact of individual depressive symptoms on impairment of psychosocial functioning. PLoS One 9, e90311.
Goodwin, G.M., 2015. The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues Clin. Neurosci. 17, 249–260.
Goularte, J.F., Serafim, S.D., Colombo, R., Hogg, B., Caldieraro, M.A., Rosa, A.R., 2021. COVID-19 and mental health in Brazil: Psychiatric symptoms in the general population. J. Psychiatr. Res. 132, 32–37.
Hemingway, H., Nicholson, A., Stafford, M., Roberts, R., Marmot, M., 1997. The impact of socioeconomic status on health functioning as assessed by the SF-36 questionnaire: the Whitehall II Study. Am. J. Public Health 87, 1484–1490.
Hirschfeld, R.M.A., 2001. The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim. Care Companion J. Clin. Psychiatry 3, 244–254.
Isvoranu, A.-M., Epskamp, S., Waldorp, L., Borsboom, D., 2022. Network Psychometrics with R: A Guide for Behavioral and Social Scientists. Routledge.
Kamenov, K., Twomey, C., Cabello, M., Prina, A.M., Ayuso-Mateos, J.L., 2017. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol. Med. 47, 1337.
Lantz, B., 2013. Machine Learning with R. Packt Publishing Ltd.
Li, Y., Aggen, S., Shi, S., Gao, J., Li, Y., Tao, M., Zhang, K., Wang, X., Gao, C., Yang, L., Liu, Y., Li, K., Shi, J., Wang, G., Liu, L., Zhang, J., Du, B., Jiang, G., Shen, J., Zhang, Z., Liang, W., Sun, J., Hu, J., Liu, T., Wang, X., Miao, G., Meng, H., Li, Y., Hu, C., Li, Y., Huang, G., Li, G., Ha, B., Deng, H., Mei, Q., Zhong, H., Gao, S., Sang, H., Zhang, Y., Fang, X., Yu, F., Yang, D., Liu, T., Chen, Y., Hong, X., Wu, W., Chen, G., Cai, M., Song, Y., Pan, J., Dong, J., Pan, R., Zhang, W., Shen, Z., Liu, Z., Gu, D., Wang, X., Liu, X., Zhang, Q., Flint, J., Kendler, K.S., 2014. The structure of the symptoms of major depression: exploratory and confirmatory factor analysis in depressed Han Chinese women. Psychol. Med. 44, 1391–1401.
Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312.
Moser, D.K., Heo, S., Lee, K.S., Hammash, M., Riegel, B., Lennie, T.A., Arslanian-Engoren, C., Mudd-Martin, G., Albert, N., Watkins, J., 2013. "It could be worse ... lot"s worse!' Why health-related quality of life is better in older compared with younger individuals with heart failure. Age Ageing 42, 626–632.
Opsahl, T., Agneessens, F., Skvoretz, J., 2010. Node centrality in weighted networks: Generalizing degree and shortest paths. Social Networks. https://doi.org/10.1016/j.socnet.2010.03.006
Rabelo-da-Ponte, F.D., Lima, F.M., Martinez-Aran, A., Kapczinski, F., Vieta, E., Rosa, A.R., Kunz, M., Czepielewski, L.S., 2020. Data-driven cognitive phenotypes in subjects with bipolar disorder and their clinical markers of severity. Psychol. Med. 1–8.
Rapoport, M.J., Feinstein, A., 2001. Age and functioning after mild traumatic brain injury: the acute picture. Brain Inj. 15, 857–864.
Rhys, H., 2020. Machine Learning with R, the tidyverse, and mlr. Simon and Schuster.
Rocha, R., Atun, R., Massuda, A., Rache, B., Spinola, P., Nunes, L., Lago, M., Castro, M.C., 2021. Effect of socioeconomic inequalities and vulnerabilities on health-system preparedness and response to COVID-19 in Brazil:

a comprehensive analysis. Lancet Glob. Health 9, e782–e792.
Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Ment. Health 3, 5.
Schoevers, R.A., Deeg, D.J.H., van Tilburg, W., Beekman, A.T.F., 2005. Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. Am. J. Geriatr. Psychiatry 13, 31–39.
Schubert, E., Rousseeuw, P.J., 2019. Faster k-Medoids Clustering: Improving the PAM, CLARA, and CLARANS Algorithms. Similarity Search and Applications. https://doi.org/10.1007/978-3-030-32047-8_16
Shen, B.-J., Fan, Y., Lim, K.S.C., Tay, H.Y., 2019. Depression, Anxiety, Perceived Stress, and Their Changes Predict Greater Decline in Physical Health Functioning over 12 Months Among Patients with Coronary Heart Disease. Int. J. Behav. Med. 26, 352–364.
Sherbourne, C.D., Wells, K.B., Meredith, L.S., Jackson, C.A., Camp, P., 1996. Comorbid anxiety disorder and the functioning and well-being of chronically ill patients of general medical providers. Arch. Gen. Psychiatry 53, 889–895.
Serafim, S.D., Goularte, J.F., Caldieraro, M.A., Lima, F. M., Dalpiaz, G., Rabelo-da-Ponte, F.D., Torrent C., Solé, B., Vieta, E., Rosa, A.R.. Validity and reliability of the Digital Functioning Assessment Short Test (D-FAST) in Brazilian sample. *Clinical Practice and Epidemiology in Mental Health* 18, 2022.
Strobl, C., Malley, J., Tutz, G., 2009. An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. Psychol. Methods 14, 323–348.
van Borkulo, C.D., van Bork, R., Boschloo, L., Kossakowski, J.J., Tio, P., Schoevers, R.A., Borsboom, D., Waldorp, L.J., 2022. Comparing network structures on three aspects: A permutation test. Psychol. Methods. https://doi.org/10.1037/met0000476
van Loo, H.M., Aggen, S.H., Kendler, K.S., 2022. The structure of the symptoms of major depression: Factor analysis of a lifetime worst episode of depressive symptoms in a large general population sample. J. Affect. Disord. 307, 115–124.
van Loo, H.M., de Jonge, P., Romeijn, J.-W., Kessler, R.C., Schoevers, R.A., 2012. Data-driven subtypes of major depressive disorder: a systematic review. BMC Med. 10, 156.
Vigo, D., Thornicroft, G., Atun, R., 2016. Estimating the true global burden of mental illness. Lancet Psychiatry 3, 171–178.
Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C.S., Ho, R.C., 2020. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int. J. Environ. Res. Public Health 17. https://doi.org/10.3390/ijerph17051729
Zahn, R., Lythe, K.E., Gethin, J.A., Green, S., Deakin, J.F.W., Young, A.H., Moll, J., 2015. The role of self-blame and worthlessness in the psychopathology of major depressive disorder. J. Affect. Disord. 186, 337–341.
Zakeri, M.A., Hossini Rafsanjanipoor, S.M., Kahnooji, M., Ghaedi Heidari, F., Dehghan, M., 2021. Generalized Anxiety Disorder During the COVID-19 Outbreak in Iran: The Role of Social Dysfunction. J. Nerv. Ment. Dis. 209, 491–496.

Figure
1

Click here to access/download;Figure(s);Figure 1.docx

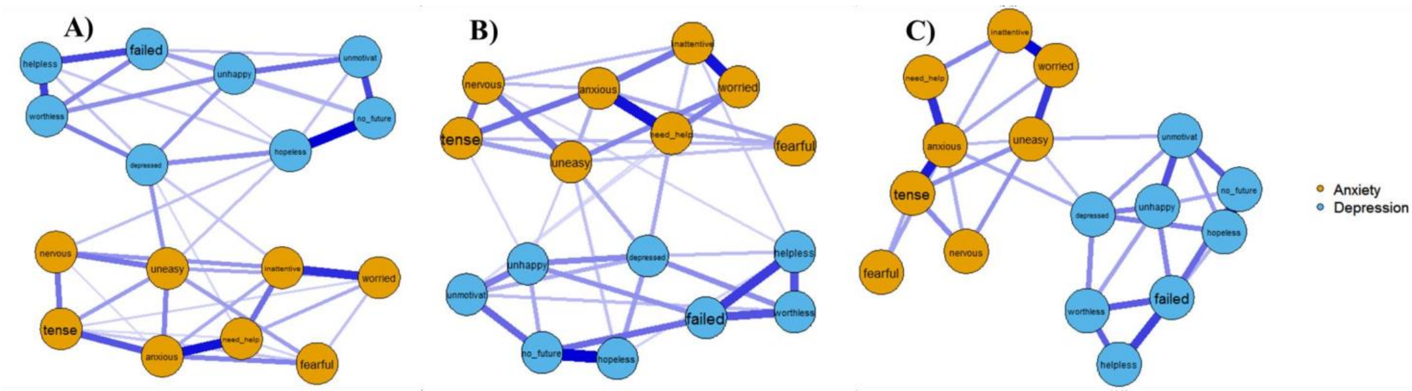

Figure 1. Networks of symptoms among three functioning clusters. A) Network of symptoms for subjects with good functioning. B) Network of symptoms for participants with intermediate functioning. C) Network of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. Different color nodes represent different PROMIS domains. Blue lines indicate a positive association between two symptoms. Thicker edges represent stronger associations and thinner edges mean weaker association. The meaning of acronyms for depressive symptoms: *worthless — I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful

— *I felt fearful*; innatentive — *I found it hard to focus on anything other than my anxiety*; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*".

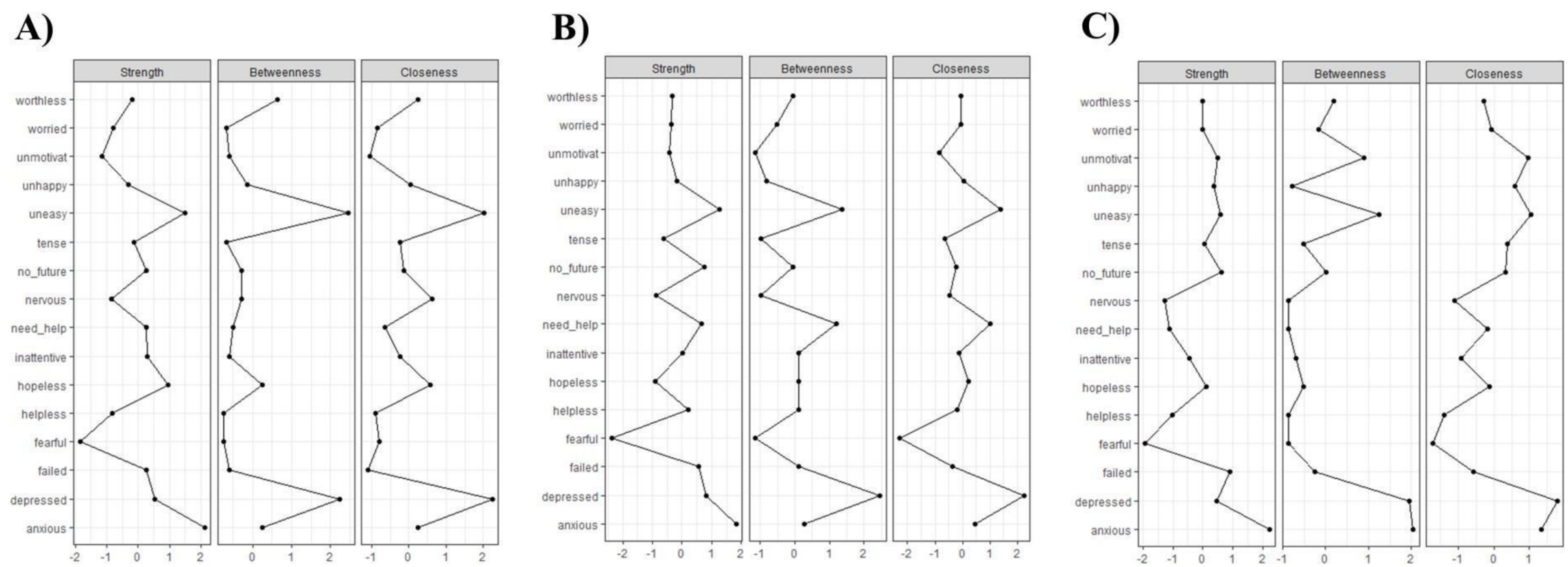

Figure 2. Centrality measures among three functioning clusters. A) Centrality measures of symptoms for subjects with good functioning. B) Centrality measures of symptoms for participants with intermediate functioning. C) Centrality measures of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. The meaning of acronyms for depressive symptoms: *worthless — I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful — *I felt fearful*; innatentive — *I*

found it hard to focus on anything other than my anxiety; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*”.

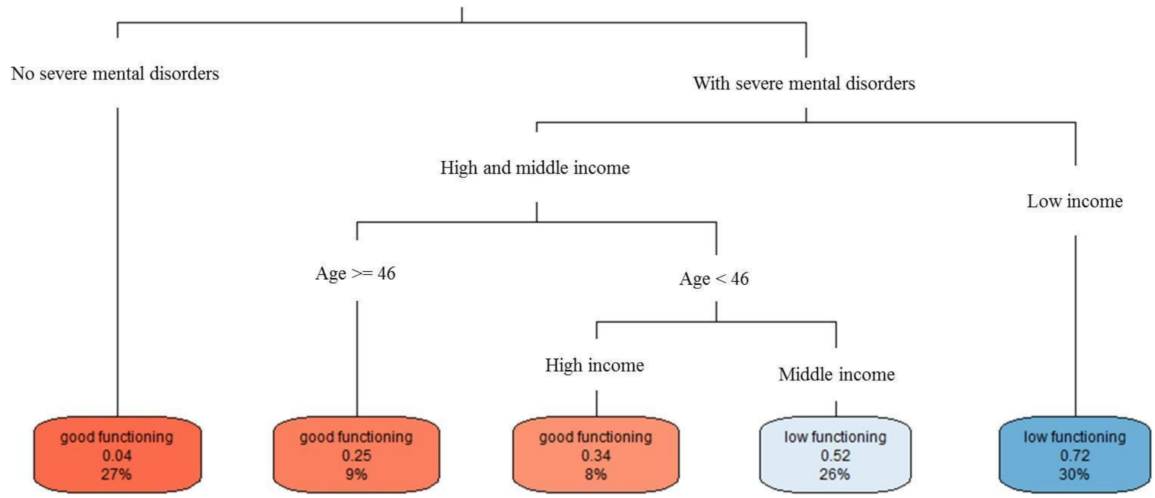

Figure 3. Decision tree using RPART algorithm to identify the clinical characteristics of subjects with good and low functioning in ~~non-clinical sample~~the general population. Each node shows three information: 1) the predicted class (good or low functioning); 2) the predicted probability of the predicted class; 3) the percentage of observation at the node in relation to the entire sample size.

Fundings

"This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) –Finance Code 001".
“This work received financial supports from Conselho Nacional de Desenvolvimento
304 Científico e Tecnológico

Author’s contribution

Conceptualization: FDRP, ARR, NV, SA. Data Curation: FDRP, ARR, FRG, SDS, SA.

Formal Analysis: FDRP, ARR, NV, SA. Investigation: FDRP, ARR, FRG, SDS, SA, MAC, EV, JARQ.

Methodology: FDRP, ARR, FRG, SDS, SA, MAC.

Project Administration: ARR, FRG, SDS, MAC.

Supervision: ARR, SA, EV, JARQ, MAC.

Validation: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS.

Visualization: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS, ED, JARQ.

Writing – Original Draft Preparation: FDRP, NV, SA. Writing –

Review&Editing: SA, ARR, ED, MAC, JARQ.

Conflict of Interest

Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

Josep Antoni Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen- Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli-Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

Norma Verdolini has received financial support for CME activities and travel funds from the following entities (unrelated to the present work): Angelini, Janssen, Lundbeck, Otsuka.

Marco Antonio Caldieraro has received grants from the following entities (unrelated to the present work): Conselho Nacional de Desenvolvimento Científico e Tecnológico, and Janssen.

The rest of authors report no biomedical financial interests or potential conflicts of interest related to the present article.

Acknowledgment

We are extremely grateful to all the participants.

Eduard Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283, PI18/00805) integrated into the Plan Nacional de I + D + I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365) and the CERCA Programme / Generalitat de Catalunya. He would like to thank the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357.

Silvia Amoretti has been supported by a Sara Borrell contract (CD20/00177), funded by Instituto de Salud Carlos III (ISCIII) and co-funded by European Social Fund "Investing in your future".

Adriane R Rosa thanks to the CNPq process 302382/2019-4. Jéferson F Goularte thanks to 300 Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES).

Figure 1

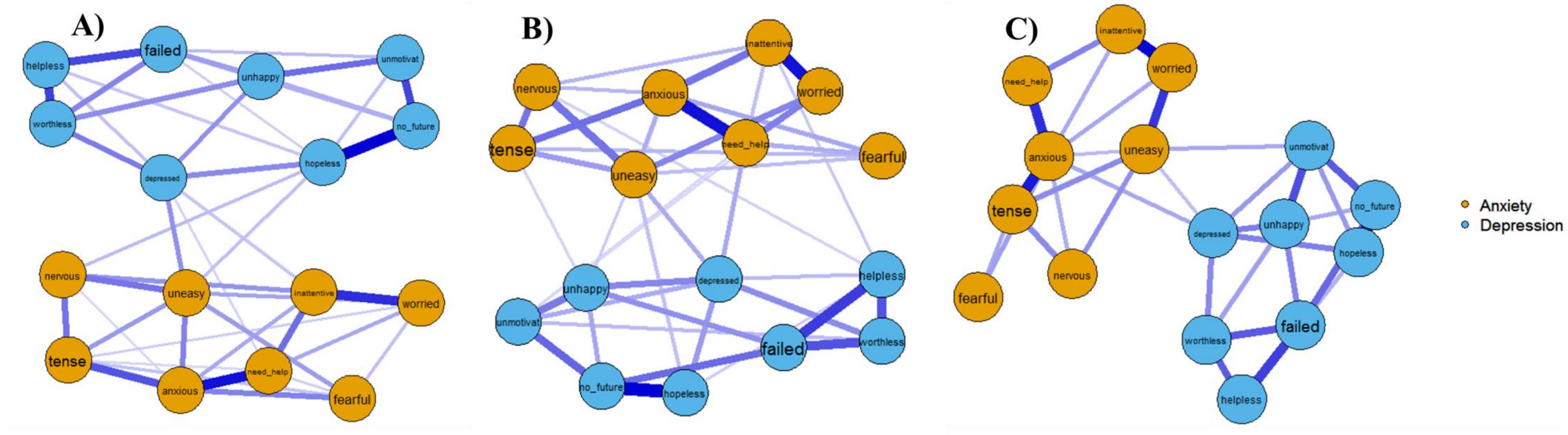

Figure 1. Networks of symptoms among three functioning clusters. A) Network of symptoms for subjects with good functioning. B) Network of symptoms for participants with intermediate functioning. C) Network of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. Different color nodes represent different PROMIS domains. Blue lines indicate a positive association between two symptoms. Thicker edges represent stronger associations and thinner edges mean weaker association. The meaning of acronyms for depressive symptoms: *worthless* — *I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful — *I felt fearful*; innatentive — *I found it hard to focus on anything other than my anxiety*; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*".

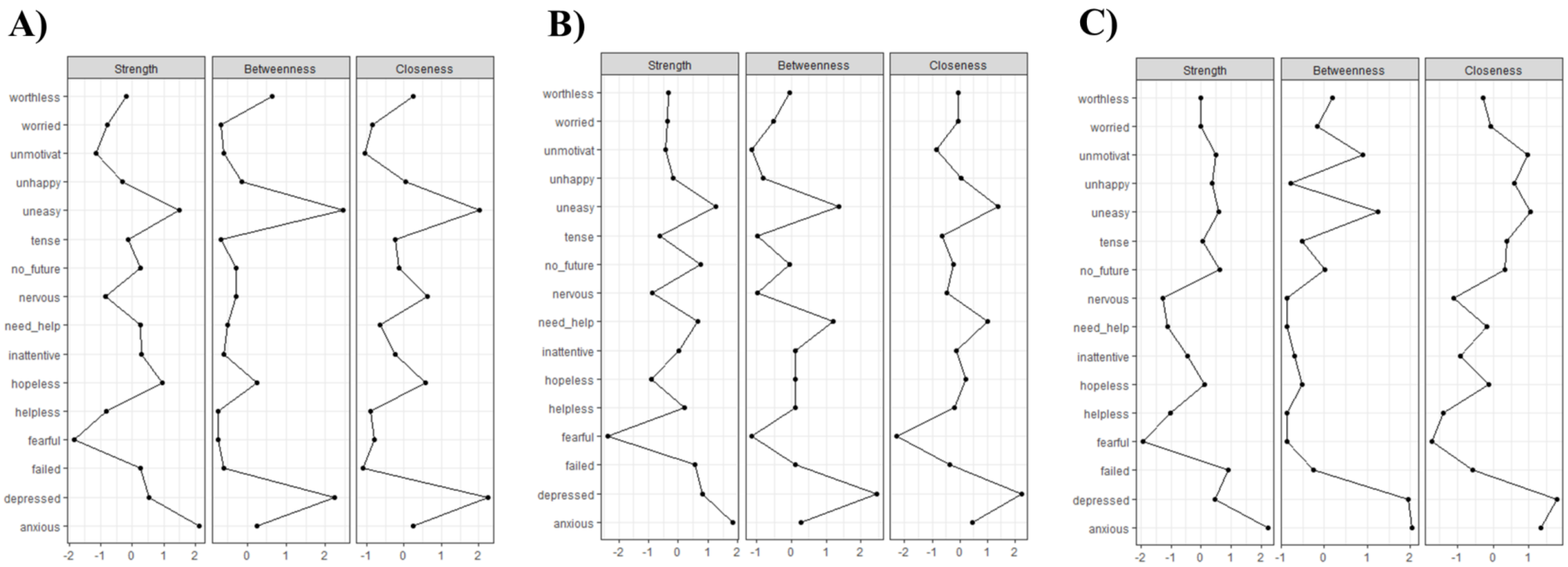

Figure 2. Centrality measures among three functioning clusters. A) Centrality measures of symptoms for subjects with good functioning. B) Centrality measures of symptoms for participants with intermediate functioning. C) Centrality measures of symptoms for subjects with low functioning. Each node represents a Reported Outcomes Measurement Information System (PROMIS) item using the mixed graphical model. The meaning of acronyms for depressive symptoms: *worthless* — *I felt worthless*; helpless — *I felt helpless*; depressed — *I felt depressed*; hopeless — *I felt hopeless*; failed — *I felt like a failure*; unhappy — *I felt unhappy*; no_future — *I felt that I had nothing to look forward*; unmotivat — *I felt that nothing could cheer me up*". The meaning of acronyms for anxious symptom: fearful — *I felt fearful*; innatentive — *I*

found it hard to focus on anything other than my anxiety; Worried — *My worries overwhelmed me*; uneasy — *I felt uneasy*; nervous — *I felt nervous*; need_help — *I felt like I needed help for my anxiety*; anxious — *I felt anxious*; Tense — *I felt tense*".

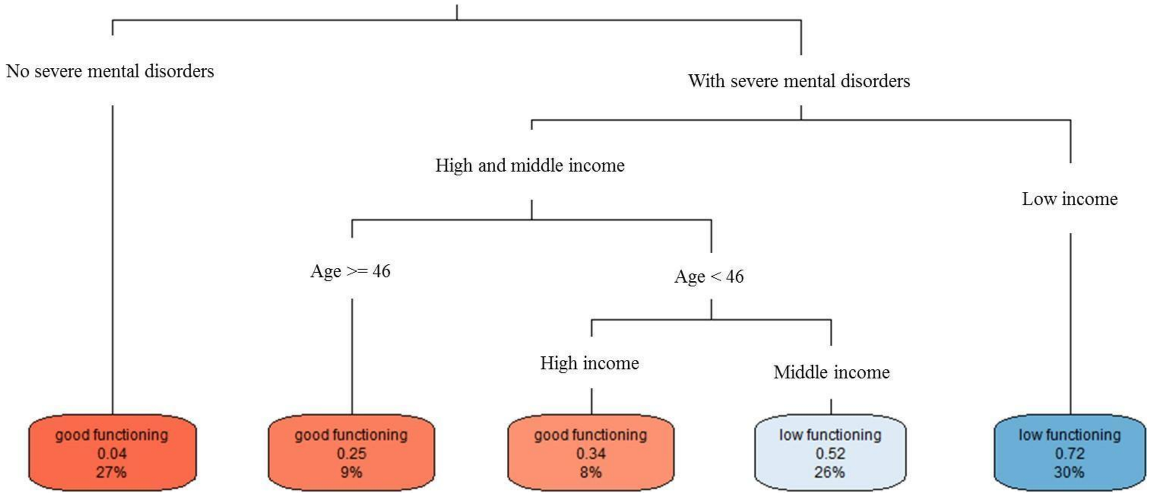

Figure 3. Decision tree using RPART algorithm to identify the clinical characteristics of subjects with good and low functioning in non-clinical sample. Each node shows three information: 1) the predicted class (good or low functioning); 2) the predicted probability of the predicted class; 3) the percentage of observation at the node in relation to the entire sample size

Fundings

"This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) –Finance Code 001".
“This work received financial supports from Conselho Nacional de Desenvolvimento
304 Científico e Tecnológico

Author's contribution

Conceptualization: FDRP, ARR, NV, SA. Data Curation: FDRP, ARR, FRG, SDS, SA.

Formal Analysis: FDRP, ARR, NV, SA. Investigation: FDRP, ARR, FRG, SDS, SA, MAC, EV, JARQ.

Methodology: FDRP, ARR, FRG, SDS, SA, MAC.

Project Administration: ARR, FRG, SDS, MAC.

Supervision: ARR, SA, EV, JARQ, MAC.

Validation: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS.

Visualization: FDRP, NV, ARR, FRG, SDS, SA, MAC, SDS, ED, JARQ.

Writing – Original Draft Preparation: FDRP, NV, SA.

Writing – Review&Editing: SA, ARR, ED, MAC, JARQ.

Conflict of Interest

Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

Josep Antoni Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli-Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

Norma Verdolini has received financial support for CME activities and travel funds from the following entities (unrelated to the present work): Angelini, Janssen, Lundbeck, Otsuka.

Marco Antonio Caldieraro has received grants from the following entities (unrelated to the present work): Conselho Nacional de Desenvolvimento Científico e Tecnológico, and Janssen.

The rest of authors report no biomedical financial interests or potential conflicts of interest related to the present article.

Acknowledgment

We are extremely grateful to all the participants.

Eduard Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283, PI18/00805; PI21/00787) integrated into the Plan Nacional de I + D + I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365) and the CERCA Programme / Generalitat de Catalunya. He would like to thank the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357.

Silvia Amoretti has been supported by a Sara Borrell contract (CD20/00177), funded by Instituto de Salud Carlos III (ISCIII) and co-funded by European Social Fund "Investing in your future".

Adriane R Rosa thanks to the CNPq process 302382/2019-4.

Jéferson F Goularte thanks to 300 Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES).

Click here to access/download
Supplementary Material
Supplementary figure 2.docx