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# *Recuperação após um Primeiro Episódio Psicótico: network analysis das relações entre a recuperação clínica e pessoal, adesão à medicação antipsicótica e apoio à recuperação*

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# Recovery in First-Episode Psychosis: a network analysis of clinical and personal recovery, antipsychotics adherence and recovery support

Recovery in Early Psychosis: network analysis

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## RESUMO

**Objetivo:** O conhecimento acerca da relação entre a recuperação clínica e pessoal num primeiro episódio psicótico é escasso. *Network analysis* é uma abordagem útil para explorar interações complexas entre variáveis associadas com diferentes dimensões da recuperação e a experiência dos doentes com os cuidados clínicos.

**Métodos:** Este estudo utilizou a *network analysis* para examinar as inter-relações entre um amplo conjunto de variáveis, abrangendo psicopatologia, funcionalidade, recuperação pessoal, adesão à medicação antipsicótica e apoio à recuperação em 49 doentes adultos com um primeiro episódio psicótico e acompanhados em regime de ambulatório por uma equipa de intervenção precoce na psicose. O *Graphical Least Absolute Shrinkage and Selection Operator* combinado com o modelo de seleção extended *Bayesian information criterion* foram utilizados para a construção da rede. A importância de nodos individuais na rede gerada foi quantificada com análises de centralidade.

**Resultados:** Do número total de doentes, 37 sujeitos (75,5%) foram considerados em remissão sintomática e 24 participantes (49,0%) atingiram critérios de recuperação clínica. A média e o desvio-padrão das pontuações da *Hope, Agency and Opportunity* foi 11,9 (2,6). A recuperação pessoal e a funcionalidade não estavam diretamente relacionadas. A relação com os profissionais de saúde mental obteve o papel mais central e teve as associações mais fortes com as variáveis da rede, como indexado pela *node strength*. Verificaram-se associações importantes entre a experiência dos doentes sobre a relação terapêutica, o apoio à recuperação e as atitudes e crenças acerca da medicação antipsicótica. Os nodos relativos aos sintomas, e.g. delírios, alucinações e embotamento afetivo, também tiveram um papel central na rede.

**Conclusões:** A perspetiva dos doentes com um primeiro episódio psicótico acerca das relações com os profissionais de saúde mental assume um papel essencial para o sucesso do tratamento. Considerar a experiência de recuperação dos doentes é crucial para melhorar os serviços de intervenção precoce na psicose.

**PALAVRAS-CHAVE**

Intervenção precoce, primeiro episódio psicótico, *network analysis*, recuperação, relação terapêutica

## ABSTRACT

**Aim:** Knowledge of the interplay between clinical and personal recovery in first-episode psychosis is scarce. Network analysis is a data-driven approach useful to explore the complex interactions among variables associated with different dimensions of recovery and patient experiences with clinical care.

**Methods:** This study employed network analysis to examine inter-relationships among a wide array of variables encompassing psychopathology, functionality, personal recovery, antipsychotics adherence and recovery support in 49 adult first-episode psychosis patients in an early psychosis outpatient unit. Graphical Least Absolute Shrinkage and Selection Operator combined with extended Bayesian information criterion model selection were used for network construction. Importance of individual nodes in a generated network was quantified by centrality analyses.

**Results:** Using broad cross-sectional criteria, 37 subjects (75.5%) were considered in symptomatic remission and 24 participants (49.0%) achieved criteria for clinical recovery. The mean and standard deviation of Hope, Agency and Opportunity scores was 11.9 (2.6). Personal recovery and functionality were not directly related. Relationship with mental health workers played the most central role and had the strongest associations with other variables of the network, as indexed by node strength. There were important associations between patients' experience of the therapeutic relationship, recovery support and the attitudes and beliefs about antipsychotic medication. Symptom nodes, e.g. delusions, hallucinations and blunted affect, also played a central role in the network.

**Conclusions:** First-episode psychosis patients' perspective of the relationship with mental health professionals has a pivotal role to the success of treatment. Considering the patients' recovery experience is crucial to improve early intervention in psychosis services.

**KEYWORDS**

Early intervention, first-episode psychosis, network analysis, recovery, therapeutic relationship

## INTRODUCTION

Psychotic disorders have extensive personal and societal impact and acting in initial stages to improve outcomes is the aim of early intervention in psychosis (EIP) (Malla & McGorry, 2019). EIP services offer multimodal interventions tailored to patients' needs and provided by a multidisciplinary mental health team. Compared to treatment-as-usual, EIP is apparently cost-effective (Aceituno, Vera, Prina, & McCrone, 2019), demonstrating superiority across several outcomes such as symptoms, hospitalizations, relapse rates, functioning and services satisfaction (Malla & McGorry, 2019; Correl et al., 2018).

To improve outcomes in first-episode psychosis (FEP), EIP programs elaborate strategies to reduce untreated psychosis and promote recovery in the critical period: 2-5 years after psychosis onset (Malla & McGorry, 2019; Fusar-Poli, McGorry, & Kane, 2017). It has been proposed that FEP recovery can be divided into three domains: (1) illness/symptomatic, focused on symptom reduction/remission; (2) social/functional, comprising societal and occupational roles, relationships and self-care; (3) personal/psychological, based on the meaning that a FEP patient attributes to their experience. These recovery dimensions can be measured using a combination of several patient-reported outcome measures (PROMs) and clinician-reported outcome measures (CROMs) (Jackson, Baggott, Bernard, Clutterbuck, Ryles, & Turner, 2019).

In a recent meta-analysis of 79 outcome studies, authors reported remission and recovery rates in FEP (Lally, Ajnakina, Stubbs, Cullinane, Murphy, Gaughran, & Murray, 2017). While remission was defined in terms of symptomatic and/or functional improvement with (narrow criteria) or without (broad criteria) a 6-month duration component, recovery was determined as symptomatic and functional improvement in social, occupational and educational domains, with a span component over two years. The meta-analysis found that 58% of FEP patients met remission criteria and 38% had criteria for recovery, over mean follow-up periods of 5.5 and 7.2 years, respectively, concluding that remission and recovery rates in FEP might be better than previously thought, and that clinical recovery stabilises after the first two years of illness.

As personal recovery is an idiographic, non-linear and self-defined process, the acronym CHIME (Connectedness, Hope and optimism about the future, Identity, Meaning in life and Empowerment) has been proposed to summarize this recovery dimension's conceptual processes (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011). Qualitative studies, focused on personal meaning of recovery in FEP, identified early recovery processes: alleviation of symptoms and associated distress; reconciling the meaning of illness experience; regaining control over experience; negotiation and

treatment acceptance (Windell, Norman, Lal, & Malla, 2015). Meaningful engagement in valued roles and social relationships are other themes described by EIP service users as components of personal recovery (Windell, Norman, & Malla, 2012; Eisenstadt, Monteiro, Diniz, & Chaves, 2012).

Different dimensions of recovery have complex inter-relationships and clinical and personal recovery outcomes are not always synchronous (Macpherson, Pesola, Leamy, Bird, Le Boutillier, Williams, & Slade, 2016). In a meta-analysis investigating the relationship between clinical and personal recovery in schizophrenia-spectrum disorders, only a small to medium association was found between different dimensions of recovery, with substantial heterogeneity between studies; psychotic symptoms and functioning had a smaller correlation with personal recovery than affective symptoms (Van Eck, Burger, Vellinga, Schirmbeck, & de Haan, 2018).

Nonetheless, knowledge of the interplay between clinical and personal recovery in FEP is scarce. To our knowledge, only the iHOPE-20, a prospective 20-year follow-up study of a FEP cohort, explored relations between remission, clinical and personal recovery (O'Keeffe et al., 2019). Authors found that psychotic symptoms' full remission and personal recovery were likely in the very long-term: 65% were in remission, 35.2% in full functional recovery and 53.7% fully recovered according to their personal recovery definition. However, this study described a complex pattern of inter-relationship between symptomatic, functional and personal dimensions of recovery, suggesting they are neither discrete constructs nor significantly related.

Network analysis (NA) is a data-driven approach useful in exploring complex interactions between variables, namely those associated with different recovery dimensions experienced by EIP services' patients; inter-relationships among variables can be constructed, estimated and visualized as a network structure (Borsboom & Cramer, 2013). By identifying the network's most central nodes, the analysis provides information on variables' relative importance to EIP processes and outcomes (Epskamp, Borsboom, & Fried, 2018).

The main aim of this study was to employ NA to examine, in FEP outpatients receiving EIP care, inter-relationships among psychopathology, functionality, personal recovery, attitudes to antipsychotic medication and recovery support. Other specific objectives were: (1) constructing a network structure and examining interactions between variables related with patient's experience of EIP interventions and different recovery outcomes; (2) identifying the generated network's most central variables, by computing centrality measures taken from graph theory.

## METHODS

### Participants

An observational transversal study was conducted in a tertiary university hospital, with patients from the Coimbra Early Psychosis Intervention Unit, a multidisciplinary EIP team offering care to individuals aged 18-40 presenting with FEP. Outpatients attending appointments between November/2019 and March/2020 were consecutively invited to participate. Patients completed data on 14 variables regarding clinical and personal recovery, patient's experience with antipsychotics and recovery support; variables were used for NA. This study was approved by the Ethical Committee of Centro Hospitalar e Universitário de Coimbra; all subjects gave written informed consent (Appendix 1).

### Assessment

Sociodemographic, service use and treatment data were extracted from clinical records. Psychiatric diagnosis was formulated by consultant psychiatrists, based on DSM-5 criteria. Clinical recovery variables were assessed with clinician-rated outcome measures (CROM) of psychotic symptoms and functionality. Personal recovery was assessed with patient-rated outcome measures (PROM). Patient-reported experience measures (PREM) were used to assess recovery support and beliefs/attitudes regarding antipsychotics.

Psychotic psychopathology was assessed with an abbreviated version of Positive and Negative Syndrome Scale: PANSS-6 (Østergaard, Lemming, Mors, Correll, & Bech, 2016). This brief scalable 6-item PANSS version includes: P1. Delusions, P2. Conceptual Disorganization, P3. Hallucinations, N1. Blunted Affect, N4. Social Withdrawal, N6. Lack of spontaneity and conversation flow (alogia). A total score $< 14$ defined symptomatic remission.

Functionality was assessed with Personal and Social Performance Scale (PSP) (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000); available data supports its reliability and validity in routine clinical and research settings (Brissos et al., 2012). Clinicians rate four dimensions: socially useful activities, (including work/study), personal and social relationships, self-care and disturbing and aggressive behaviours, with a total score between 0-100. A PSP score $> 70$ defined high-functioning patients.

Personal Recovery was assessed with Hope, Agency and Opportunity (HAO) (Newman-Taylor, Garner, Vernon-Wilson, Paas, Herbert, & Au-Yeung, 2017), a 4-item self-reported measure developed with input from mental patients. The questionnaire incorporates 3 outcome items (Hope, Sense of Control and Opportunity) and an

experience item (Relationships with mental health professionals). Items are rated on a 5-point scale from 0-4, with a total score varying between 0–16; higher scores indicate greater recovery.

Recovery Support was assessed with Brief INSPIRE (Williams, Leamy, Bird, Le Boutillier, Norton, Pesola, & Slade, 2015), a 5-item measure designed to assess a service user's experiences of support from a mental health worker in their recovery. This brief measure includes one item for each CHIME recovery processes (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011). Brief INSPIRE's total score ranges from 0 (low recovery support) to 100 (high recovery support).

Antipsychotic medication adherence was assessed with the Antipsychotic Medication Beliefs and Attitudes Scale (AMBAS) (Martins et al., 2019). It is a 12-item self-report instrument designed to assess several aspects influencing antipsychotic adherence in psychotic patients. Exploratory factor analysis supported a two-factor solution: (1) the influence of different barriers to medication adherence; (2) medication's perceived positive effects. Participants rate the extent of their agreement with statements using a 5-point Likert scale from 0-4; higher results reflect greater medication adherence.

## Statistical Analysis

### Network Construction and Analysis

Fourteen variables - including six PANSS-6 symptom items, four outcome and experience HAO items, Brief INSPIRE score, PSP score and the two AMBAS factors - were selected for network analyses. In a network, each variable was represented as a node, and associations between nodes were represented as edges. We then constructed a partial correlation network, where relationships between two nodes were estimated after controlling the influence of all other network variables (i.e. conditional independence associations), using the graphical Least Absolute Shrinkage and Selection Operator (LASSO) (Friedman, Hastie, & Tibshirani, 2008), in combination with extended Bayesian information criterion (EBIC) model selection (Chen & Chen, 2008). Graphical LASSO is a regularization technique that limits spurious (false-positive) edges by assigning penalties to shrink small correlations to exactly zero, and thereby generating a more interpretable and sparse network (Epskamp, Borsboom, & Fried, 2018; Friedman, Hastie, & Tibshirani, 2008). EBIC is a goodness-of-fit measure for model selection and uses hyperparameter $\gamma$ to control its preference for more parsimonious models with fewer edges (Chen & Chen, 2008). We set hyperparameter $\gamma$ to 0.5, shown to yield accurate network estimations, with a good balance between

sensitivity and specificity in identifying true edges (Foygel & Drton, 2010). The network layout was derived from the Fruchterman–Reingold algorithm (Fruchterman & Reingold, 1991), which places nodes with stronger and more numerous associations more centrally within the network, peripherally positioning weakly connected nodes.

To assess and quantify individual nodes' importance in a generated network, we computed three centrality indices of degree, closeness and betweenness for each node (Newman, 2018; Opsahl, Agneessens, & Skvoretz, 2010). Node degree is calculated as the sum of edge weights connected to a node, quantifying how well a node is directly connected to others. Closeness is the inverse of the sum of the shortest paths from a node to all other nodes, measuring how well one node is indirectly connected to others. Betweenness measures the number of times a node lies on the shortest paths between two other nodes, quantifying how important a node is in connecting other nodes. Network construction, visualization, and centrality analyses were implemented in JASP (version 0.11.1; JASP Team, 2019); analysis and graphs performed are based on R-packages bootnet (Epskamp, Borsboom, & Fried, 2018) and qgraph (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012).

### Estimation of network accuracy and stability

First, we estimated edge-weights accuracy by calculating their 95% confidence intervals (CIs) derived from 1000 non-parametric bootstrap samples. Second, we evaluated centrality indices' stability using case-dropping subset bootstrap procedure, in which indices are repeatedly calculated from data subsets with increasing proportions of dropped subjects. Third, given the study's exploratory nature, we conducted a simulation with the *netSimulator* function in the *bootnet* package, using the estimated refitted network to gain insight of the sensitivity and specificity of the network's structure, the correlation of edge-weights, and centrality indices between 'true' and estimated networks at different sample sizes (Epskamp & Fried, 2018).

## RESULTS

### Study sample characteristics

Among 51 invited patients, 49 accepted; 42 (85.7%) patients were male. Sample's mean age was 27.6 years (S.D.=6.8), and about 1 out of 5 (20.4%) patients were not in education, employed or in training (NEET). Mean EIP team follow-up was 28.1 months (S.D.=9.2). Most subjects were taking atypical antipsychotics (91.8%), many (42.9%) using injectable long-acting antipsychotics. Using broad cross-sectional criteria, 37 subjects (75.5%) were in symptomatic remission; 24 participants (49.0%) achieved clinical recovery criteria. Data on socio-demographic, clinical, service use, experience and outcome measures are summarized in **Table 1**.

### Network Structure and Analysis

Estimated network is illustrated in **Figure 1**. We obtained a network with 14 nodes and 47 non-zero edges, with a sparsity of 0.484. Nodes related to functional recovery and personal recovery outcomes did not display direct connections. Nodes within negative symptoms domain were highly interconnected; two nodes (social withdrawal and alogia) had important negative connections with functionality. This node had an inverse association with hallucinations; no connections were found between functionality and other positive symptoms. Personal recovery outcomes had important connections with positive symptoms (especially delusions), with a direct and inverse association, respectively, with HAO's Relationship experience and Hope outcome nodes. Associations between negative symptoms and HAO nodes were weak. HAO Relationship node exhibited important positive connections with Recovery support and both Antipsychotic Adherence nodes. AMBAS' positive beliefs had a positive connection with hallucinations, being negatively associated with conceptual disorganization. Besides a strong connection with the HAO Relationship node, recovery support had weaker positive connections with Antipsychotic Adherence nodes, and weak inverse associations with social withdrawal and blunted affect.

Centrality plot is displayed in **Figure 2**. HAO Relationship node had the highest node degree and relatively high betweenness and closeness indices. HAO Relationship node connected with HAO Control and Opportunity nodes, Delusions, Recovery Support and Antipsychotic Adherence nodes. By a weak inverse association with Social Withdrawal, it established an indirect path between negative symptoms with Functionality and Personal recovery outcome nodes. In clinical recovery outcome domains, positive symptoms had relatively high degree, betweenness and closeness

indices. Delusions node had the highest betweenness and closeness indices of the network. This node had strong positive connections with other positive symptoms, and important connections with HAO Relationship node (positive) and HAO Hope node (negative). Blunted affect also had a high node degree, with strong positive connections to other negative symptoms and the conceptual disorganization node. This node had weaker positive associations with delusions and HAO Hope nodes, and inverse connections with Barriers to Adherence and Recovery Support nodes.

**Network Accuracy and Stability**

As shown in **Figure 3**, bootstrapped 95% CIs were overall large, indicating most edges' order in the network should be interpreted with care. Regarding stability of centrality indices represented in **Figure 4**, node degree (strength) was the centrality measure that retained an acceptable correlation with subsets containing 30% of the cases; node degree should be interpreted cautiously. Other centrality indices were not stable from the beginning of case dropping, and their values were not interpretable with current sample size. Simulation results, comparing network accuracy and the estimated network's stability with putative networks of greater sample sizes, are illustrated in **Figure 5.** The specificity, sensitivity and correlation between true and estimated networks were acceptable with the sample's size. Smaller correlations between true and estimated centrality indices advise careful interpretation.

## DISCUSSION

To our knowledge, this is the first study employing NA to explore relationships between symptomatic, functional and personal recovery outcomes with experience of care (medication, relationship with professionals and recovery support) in FEP patients receiving EIP care. We found that functional and personal recovery outcomes were not directly connected, and that functionality was associated with negative symptoms and hallucinations. Some symptomatic nodes (delusions, hallucinations, blunted affect) had a central role in the network, with direct and indirect links between different domains of recovery. Patients' experience of the relationships with mental health professionals had the greatest node degree, with important connections with antipsychotic adherence, recovery support, and both symptomatic and personal recovery outcomes.

A single study had employed NA to explore inter-relationships between psychopathology, premorbid adjustment, cognition and psychosocial functioning in FEP (Chang et al., 2019). Authors found connections between symptomatic and functional domains, with a strong inverse association between amotivation and psychosocial functioning, and weaker links with diminished expression and positive symptoms, supported by our findings. Negative symptoms usually cohere into two distinct, yet related, subdomains: diminished expression, consisting of affective flattening and poverty of speech; and amotivation, that includes social withdrawal, in addition of avolition, apathy, and hedonic deficits (Madeira, Caldeira, Bajouco, Pereira, Martins, & Macedo, 2016). In our study, functioning had stronger inverse associations with social withdrawal, and weaker inverse associations with alogia, without direct links to blunted affect, supporting specific relationships between different negative symptoms domains and functionality.

The estimated network had no direct links between functional outcome and personal recovery outcomes. The iHOPE-20 study (O'Keeffe et al., 2019) is the only FEP incidence cohort study assessing symptomatic, functional and personal recovery domains. Our rates of symptomatic remission, clinical recovery and scores of personal recovery measures are in line with this prospective study, suggesting relatively favourable outcomes in different FEP recovery domains. iHope-20's results suggested a complex relationship between symptomatic remission status, full functional recovery status and personal recovery; agreement between symptomatic remission status and personal recovery was moderate and higher than the association between full functional recovery and personal recovery. Our estimated network supports these findings: personal recovery outcome nodes connected with some positive and negative symptoms, having no direct connections with functionality.

Two other cross-sectional studies explored relationships between personal recovery outcomes and symptoms, among other factors, using regression methods (Madeira, Caldeira, Bajouco, Pereira, Martins, & Macedo, 2016; Norman, Windell, Lynch, & Manchanda, 2013). In these studies, psychotic symptoms, especially negative, were correlated with personal recovery outcomes; however, perceived relational evaluation (Madeira, Caldeira, Bajouco, Pereira, Martins, & Macedo, 2016) and quality of life (Norman, Windell, Lynch, & Manchanda, 2013) were higher predictors of personal recovery. Our study did not include such variables, but our network showed stronger links between some positive symptoms and recovery outcomes, especially an inverse association between delusions and hope. Connections between negative symptoms and personal recovery outcomes were weaker.

An important finding of our study is the centrality in the estimated network of patients' perception of their relationship with mental health professionals, emphasizing the impact of therapeutic alliance in recovery. This finding is supported by systematic reviews showing that a positive therapeutic relationship with psychotic patients was associated with better clinical and recovery outcomes (Priebe, Richardson, Cooney, Adedeji, & McCabe, 2011; Browne, Nagendra, Kurtz, Berry & Penn, 2019). In a study of FEP patients who received a specialized EIP program (NAVIGATE), better therapeutic alliances related with improved mental health recovery and better symptomatic outcomes (Browne, Mueser, Meyer-Kalos, Gottlieb, Estroff, & Penn, 2019). Other FEP studies showed that patient's ratings of their therapeutic relationship predict social inclusion through hopefulness (Berry & Greenwood, 2015). Meta-synthesis that reviewed qualitative studies about essential ingredients (Tindall, Simmons, Allott, & Hamilton, 2018) and experience (Loughlin, Bucci, Brooks, & Berry, 2020) of FEP patients' engagement with EIP teams also identified the quality of therapeutic relationship with a staff member as a key topic for users.

These convergent findings from studies with different research designs bring important practical implications to EIP teams' processes of care, stressing the relevance of non-specific components of care (Priebe, Conneely, McCabe, & Bird, 2020), namely how mental health professionals communicate with patient (Pestana-Santos, Loureiro, Santos, & Carvalho, 2018). In our study, experience with therapeutic relationship was not only connected to symptomatic and personal recovery outcome nodes, but also had important connections with process measures like adherence to antipsychotics and recovery support. Training psychiatrists' communication (McCabe et al., 2016), besides patient-centred and solution-focused methods to structure communication, like

DIALOG+ (Priebe et al., 2015; Omer, Golden, & Priebe, 2016), could prove helpful for EIP teams' operation.

EIP programs are complex interventions with different components grounded in evidence-based practices; but teams' performance can be assessed with fidelity measures (Addington et al., 2018). In many countries, implementing EIP multidisciplinary teams with high levels of fidelity is a daunting challenge (Coentre & Levy, 2020). The network approach introduces a novel conceptualization of treatment interventions that could facilitate a parsimonious selection of EIP components of care, adapted to local contexts and resources. In a network model, there are three factors that influence its dynamics: the nodes in the network, the connections in the network and the external field of factors outside of the network that influence it (Isvoranu, Boyette, Guloksuz, & Borsboom, 2017). From a network perspective, we can consider three types of intervention: (1) node interventions (e.g. antipsychotics targeting positive symptoms); (2) edge interventions (e.g. contextual behavioural therapies) (Martins, Carvalho, Macedo, Pereira, Braehler, Gumley, & Castilho, 2018) that could target connections between symptoms or between symptomatic and personal recovery outcomes); (3) field interventions (e.g. cannabis use interventions addressing risk factors that influence the dynamic of the network). Empirical studies examining different interventions' influence on FEP symptom and process-outcome networks are an important future venue of research.

The major limitation of this exploratory study is its relatively small sample that hampers some NA parameters. Additionally, the absence of a treatment-as-usual group, e.g. of psychotic patients receiving non-EIP care, precludes generalization of these findings outside specialized EIP units.

## CONCLUSIONS

Addressing FEP patients' perspective on their recovery is not only feasible, but a key component to treatment personalization, delivering adequate and evidence-based EIP care that can effectively improve prognosis and daily functioning of individuals with psychosis (Martins, Soares, Bem-Haja, Roque, & Madeira, 2015). Although recent psychological models for psychosis have valued the importance to everyday functioning of how patients relate psychologically with symptoms (Martins et al., 2018), the centrality of FEP patients' perception of their alliance with mental health professionals remains a pivotal ingredient to EIP success.

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## CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

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## TABLES

**Table I: Socio-demographic, clinical and mental health service data**

| Variables | Mean (S.D.)/N (%) |
|---|---|
| **Socio-demographic variables** | |
| Age | 27.6 (6.8) |
| Male gender | 42 (85.7) |
| NEET status | 10 (20.4) |
| **Mental health service use variables** | |
| Follow-up, months | 28.1 (19.2) |
| Hospitalization in the last 2 years | 21 (42.9) |
| **Antipsychotic treatment variables** | |
| Use of second-generation antipsychotic | 45 (91.8) |
| Use of LAI or depot antipsychotic | 21 (42.9) |
| DDD | 0.98 (0.62) |
| **Clinician Rated Outcome Measures (CROM)** | |
| PANSS-6 | 10.8 (4.3) |
| PSP | 73.9 (14.3) |
| Symptomatic remission † | 37 (75.5) |
| Clinical Recovery ‡ | 24 (49.0) |
| **Patient Rated Outcome Measures (PROM)** | |
| HAO | 11.9 (2.6) |
| **Patient Rated Experience Measures (PREM)** | |
| Brief INSPIRE | 80.4 (17.7) |
| AMBAS Barriers to adherence | 24.4 (4.9) |
| AMBAS Positive Beliefs about medication | 12.2 (3.8) |

† **Broad Criteria for Symptomatic remission:** cross-sectional PANSS-6 score less than 14; ‡ **Broad criteria for Clinical Recovery:** cross-sectional PANSS-6 score less than 14 and PSP score more than 70

**AMBAS** Antipsychotic Medication Beliefs and Attitudes Scale; **DDD** Defined Daily Doses (Leucht, Samara, Heres, & Davis, 2016); **HAO** Hope, Agency and Opportunity; **LAI** Long Acting Injection; **NEET** Not in Employment, Education and Training; **PANSS-6** Six-item Positive and Negative Symptom Scale; **PSP** Personal and Social Performance Scale

## FIGURE LEGENDS

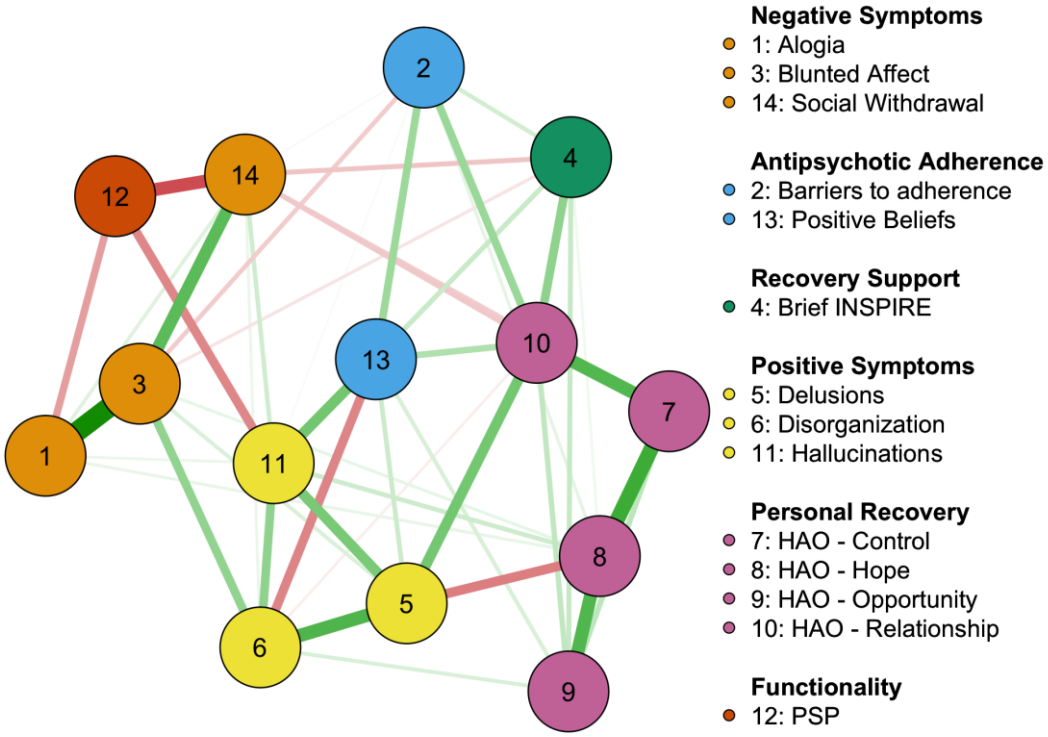


**Figure 1** Network of psychopathology, functionality, personal recovery, antipsychotic medication adherence and recovery support variables. This is a network structure of 14 study variables. Each node represents a study variable and each edge represents a significant association between two nodes. Edge thickness reflects the magnitude of an association (thicker lines indicate stronger associations). Green lines denote positive associations, while red lines denote negative associations.

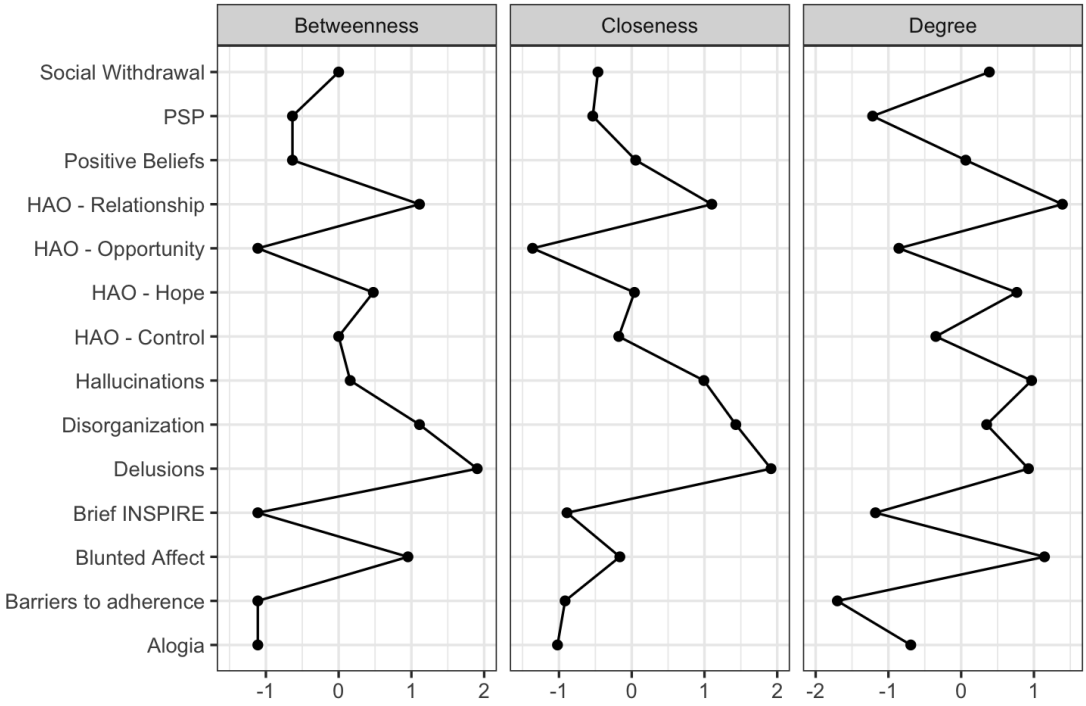


**Figure 2** Centrality indices of study variables within the network. Centrality indices of node strength, closeness and betweenness are shown as standardized z-scores.

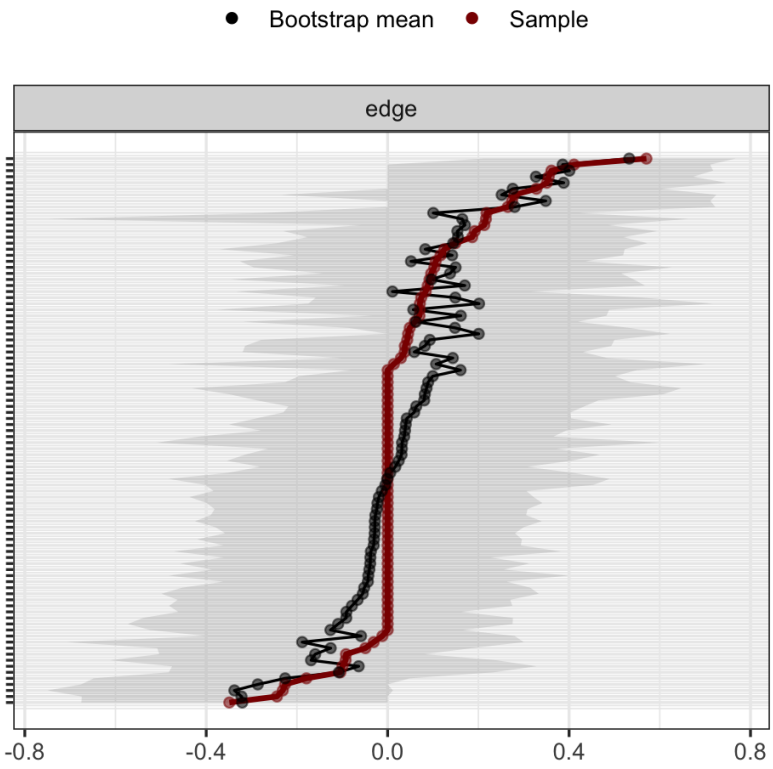


**Figure 3** Bootstrapped confidence intervals of estimated edge-weights for the estimated network. The red line indicates the sample values and the grey area the bootstrapped CIs. Each horizontal line represents one edge of the network, ordered from the edge with the highest edge-weight to the edge with the lowest edge-weight.

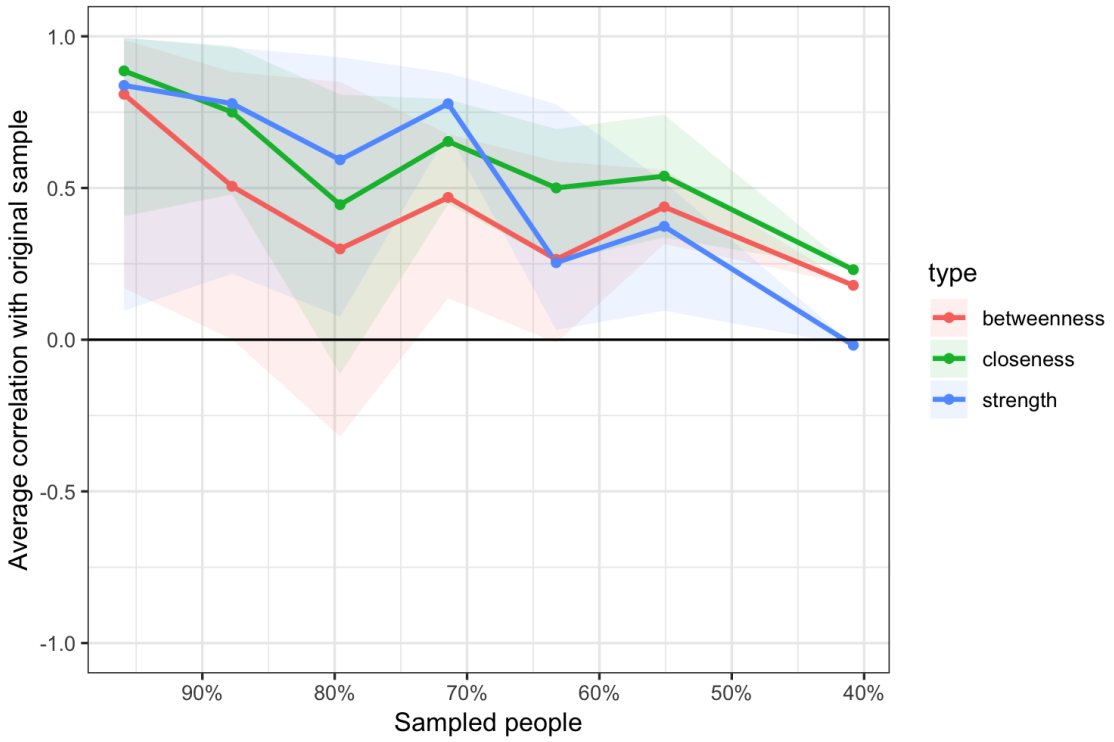


**Figure 4** Average correlations between centrality indices of networks sampled with people dropped and the original sample. Lines indicate the means and areas indicate the range from the 2.5th quantile to the 97.5th quantile.

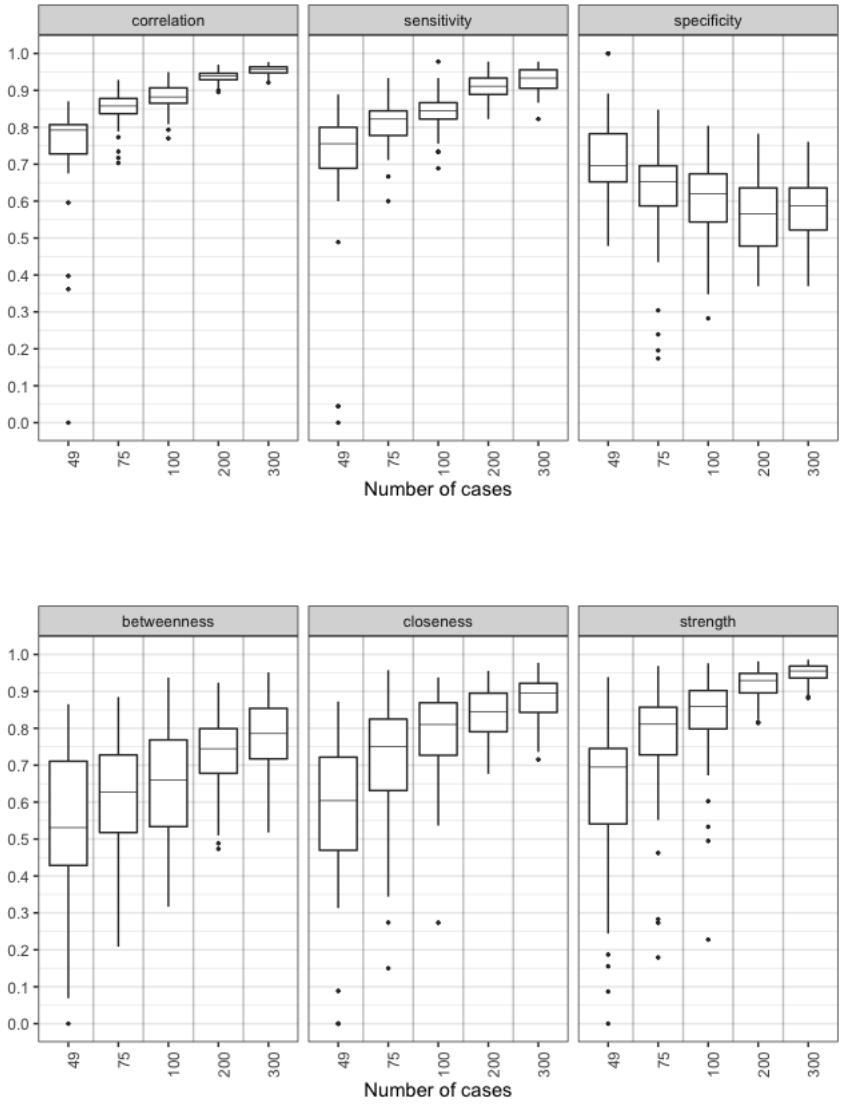


**Figure 5** Simulation results using the estimated refitted network as true network structure. The top panel shows the sensitivity (true positive rate), specificity (true negative rate) and correlation between true and estimated networks, and the bottom panel shows the correlation between true and estimated centrality indices.

# APPENDICES

## Appendix 1 Informed consent

The title was altered due to the change in the statistical analysis.

**TÍTULO DO PROJECTO DE INVESTIGAÇÃO:** Recuperação pessoal após um primeiro episódio psicótico: um estudo exploratório das associações com a intervenção clínica e a integração na comunidade

**PROTOCOLO Nº**

| | |
|---|---|
| **PROMOTOR (Entidade ou Pessoa(s)) que propõe(m) o estudo)** | Faculdade de Medicina da Universidade de Coimbra |
| **INVESTIGADOR COORDENADOR** | Elisabete Sofia Torres Branco |
| **CENTRO DE ESTUDO** | Centro de Responsabilidade Integrada de Psiquiatria (CRIP) do Centro Hospitalar Universitário de Coimbra (CHUC) |
| **INVESTIGADOR PRINCIPAL** | Elisabete Sofia Torres Branco |
| **MORADA** | Faculdade de Medicina da Universidade de Coimbra<br>Rua Larga, nº2<br>3000-370 Coimbra |
| **CONTACTO TELEFÓNICO** | 927304226 |

**NOME DO DOENTE**
**(LETRA DE IMPRENSA)** _____

É convidado(a) a participar voluntariamente neste estudo porque se encontra a ser acompanhado(a) na consulta de Primeiro Episódio Psicótico do CRIP do CHUC. Este procedimento é chamado consentimento informado e descreve a finalidade do estudo, os procedimentos, os possíveis benefícios e riscos. A sua participação poderá contribuir para melhorar o conhecimento sobre como se processa a recuperação pessoal após tratamento por um primeiro episódio psicótico, o que, por sua vez, poderá contribuir para melhorar os cuidados clínicos que receberá e que serão prestados aos doentes com situações idênticas à sua.
Receberá uma cópia deste Consentimento Informado para rever e solicitar aconselhamento de familiares e amigos. O Investigador ou outro membro da sua equipa irá esclarecer qualquer dúvida que tenha sobre o termo de consentimento e também alguma palavra ou informação que possa não entender.
Depois de compreender o estudo e de não ter qualquer dúvida acerca do mesmo, deverá tomar a decisão de participar ou não. Caso queira participar, ser-lhe-á solicitado que assine e date este formulário. Após a sua assinatura e a do Investigador, ser-lhe-á entregue uma cópia. Caso não

queira participar, não haverá qualquer penalização nos cuidados que irá receber.

## 1. INFORMAÇÃO GERAL E OBJECTIVOS DO ESTUDO

Este estudo irá decorrer no CRIP do CHUC, em colaboração com a Faculdade de Medicina da Universidade de Coimbra, com o objetivo de avaliar o processo de recuperação pessoal após tratamento por um primeiro episódio psicótico, explorando as associações entre a recuperação pessoal, a recuperação clínica, o apoio à recuperação pessoal, o tratamento antipsicótico e a integração na comunidade.

Trata-se de um estudo observacional, em que os doentes acompanhados na consulta de Primeiro Episódio Psicótico do CRIP do CHUC serão convidados a preencher questionários que medem o processo de recuperação pessoal, o estado sintomático e funcional, a adesão ao tratamento antipsicótico, o apoio à recuperação e a integração na comunidade, pelo que não será feita nenhuma alteração na sua medicação ou tratamentos habituais.

Este estudo foi aprovado pela Comissão de Ética do Centro Hospitalar e Universitário de Coimbra (CHUC) de modo a garantir a proteção dos direitos, segurança e bem-estar de todos os doentes ou outros participantes incluídos e garantir prova pública dessa proteção.

Como participante neste estudo beneficiará da vigilância e apoio do seu médico, garantindo assim a sua segurança.

Este estudo tem por objetivo avaliar o processo de recuperação pessoal após tratamento por um primeiro episódio psicótico, explorando as associações entre a recuperação pessoal, a recuperação clínica, o apoio à recuperação pessoal, o tratamento antipsicótico e a integração na comunidade.

## 2. PROCEDIMENTOS E CONDUÇÃO DO ESTUDO

### 2.1. Procedimentos

Os doentes acompanhados na consulta de Primeiro Episódio Psicótico do CRIP do CHUC serão convidados a preencher questionários que medem o processo de recuperação pessoal, o estado sintomático e funcional, a adesão ao tratamento antipsicótico, o apoio à recuperação e a integração na comunidade. Um médico do estudo realizará uma revisão da sua história médica recente e registará a sua medicação.

### 2.2. Calendário das visitas/ Duração (exemplo)

Este estudo consiste numa visita única com duração de cerca de 30 minutos. A seguir faz-se uma descrição do estudo:

**Descrição dos Procedimento (exemplo):**

Serão realizados os seguintes procedimentos/exames:

- Positive and Negative Syndrome Scale-6 (PANNS-6)

- Personal and Social Performance (PSP) Scale
- INSPIRE Brief
- Psychopharmacological Medication Beliefs and Attitudes Scale (PMBAS)
- Escala de Integração Comunitária de Adultos com Problemas Psiquiátricos (EIC-APP)
- Hope, Control and Opportunity Questionnaire

**2.3. Tratamento de dados/ Randomização**

Serão exploradas as associações entre as diferentes variáveis, com recurso a diferentes tipos de análise estatística.

**3. RISCOS E POTENCIAIS INCONVENIENTES PARA O DOENTE**

Com a aplicação dos diferentes questionários não são previsíveis quaisquer riscos ou potenciais inconvenientes, à exceção do tempo despendido com o seu preenchimento.

**4. POTENCIAIS BENEFÍCIOS**

Este estudo tem a vantagem de estudar como se processa a recuperação pessoal após tratamento por um primeiro episódio psicótico, o que poderá contribuir para uma melhor informação dos médicos de forma a melhorar os cuidados clínicos que receberá e que serão prestados aos doentes com situações idênticas à sua.

**5. NOVAS INFORMAÇÕES**

Ser-lhe-á dado conhecimento de qualquer nova informação que possa ser relevante para a sua condição ou que possa influenciar a sua vontade de continuar a participar no estudo.

**7. SEGURANÇA**

Durante a participação, não é expectável que, da realização do estudo, incorram riscos que comprometam a sua segurança.

**8. PARTICIPAÇÃO / ABANDONO VOLUNTÁRIO**

É inteiramente livre de aceitar ou recusar participar neste estudo. Pode retirar o seu consentimento em qualquer altura sem qualquer consequência para si, sem precisar de explicar as razões, sem qualquer penalidade ou perda de benefícios e sem comprometer a sua relação com o Investigador que lhe propõe a participação neste estudo. Ser-lhe-á pedido para informar o Investigador se decidir retirar o seu consentimento.

**9. CONFIDENCIALIDADE**

Os seus registos manter-se-ão confidenciais e anonimizados de acordo com os regulamentos e leis aplicáveis. Se os resultados deste estudo forem publicados a sua identidade manter-se-á confidencial.

Ao assinar este Consentimento Informado autoriza este acesso condicionado e restrito.

Pode ainda em qualquer altura exercer o seu direito de acesso à informação. Pode ter também acesso à sua informação médica diretamente ou através do seu médico neste estudo. Tem também o direito de se opor à transmissão de dados que sejam cobertos pela confidencialidade profissional.

Os registos médicos que o identificarem e o formulário de consentimento informado que assinar serão verificados para fins do estudo pelo promotor e/ou por representantes do promotor. A Comissão de Ética responsável pelo estudo pode solicitar o acesso aos seus registos médicos para assegurar-se que o estudo está a ser realizado de acordo com o protocolo. Não pode ser garantida confidencialidade absoluta devido à necessidade de passar a informação a essas partes.

Ao assinar este termo de consentimento informado, permite que as suas informações médicas neste estudo sejam verificadas, processadas e relatadas conforme for necessário para finalidades científicas legítimas.

**Confidencialidade e tratamento de dados pessoais**

Os dados pessoais dos participantes no estudo, incluindo a informação médica ou de saúde recolhida ou criada como parte do estudo, (tais como registos médicos ou resultados de testes), serão utilizados para condução do estudo, designadamente para fins de investigação científica relacionados com a patologia em estudo.

Ao dar o seu consentimento à participação no estudo, a informação a si respeitante, designadamente a informação clínica, será utilizada da seguinte forma:

1. O promotor, os investigadores e as outras pessoas envolvidas no estudo recolherão e utilizarão os seus dados pessoais para as finalidades acima descritas.
2. Os dados do estudo, associados às suas iniciais ou a outro código que não o(a) identifica diretamente (e não ao seu nome) serão comunicados pelos investigadores e outras pessoas envolvidas no estudo ao promotor do estudo, que os utilizará para as finalidades acima descritas.
3. Os dados do estudo, associados às suas iniciais ou a outro código que não permita identificá-lo(a) diretamente, poderão ser comunicados a autoridades de saúde nacionais e internacionais.
4. A sua identidade não será revelada em quaisquer relatórios ou publicações resultantes deste estudo.
5. Todas as pessoas ou entidades com acesso aos seus dados pessoais estão sujeitas a sigilo profissional.
6. Ao dar o seu consentimento para participar no estudo autoriza o promotor e seus colaboradores, a aceder aos dados constantes do seu processo clínico, para conferir a informação recolhida e registada pelos investigadores, designadamente para assegurar o rigor dos dados que lhe dizem respeito e para garantir que o estudo se encontra a ser desenvolvido corretamente e que os dados obtidos são fiáveis.

7. Nos termos da lei, tem o direito de, através de um dos médicos envolvidos no estudo/estudo, solicitar o acesso aos dados que lhe digam respeito, bem como de solicitar a retificação dos seus dados de identificação.
8. Tem ainda o direito de retirar este consentimento em qualquer altura através da notificação ao investigador, o que implicará que deixe de participar no estudo/estudo. No entanto, os dados recolhidos ou criados como parte do estudo até essa altura que não o(a) identifiquem poderão continuar a ser utilizados para o propósito de estudo, nomeadamente para manter a integridade científica do estudo, e a sua informação médica não será removida do arquivo do estudo.
9. Se não der o seu consentimento, assinando este documento, não poderá participar neste estudo. Se o consentimento agora prestado não for retirado e até que o faça, este será válido e manter-se-á em vigor.

**10. COMPENSAÇÃO DO PARTICIPANTE**

Este estudo é da iniciativa do investigador e, por isso, se solicita a sua participação sem uma compensação financeira para a sua execução, tal como também acontece com os investigadores e o Centro de Estudo. Não haverá igualmente qualquer custo para o participante pela sua participação neste estudo.

**11. COMPENSAÇÃO DO CENTRO DE ESTUDO / INVESTIGADOR**

O Centro de Estudo não receberá uma compensação financeira pela realização do estudo. Os Investigadores não receberão uma compensação financeira pelo seu trabalho na realização do estudo.

**12. CONTACTOS**

Se tiver perguntas relativas aos seus direitos como participante deste estudo, deve contactar:
Presidente da Comissão de Ética do CHUC
Centro Hospitalar e Universitário de Coimbra
Praceta Mota Pinto, 3000 075 Coimbra
Telefone: 239 400 400
e-mail: secetica@chuc.min-saude.pt

Se tiver questões sobre este estudo deve contactar:
Elisabete Sofia Torres Branco
Faculdade de Medicina da Universidade de Coimbra - Rua Larga, nº2, 3000-370 Coimbra
Telefone: 927304226
email: sofia.elisah@gmail.com

NÃO ASSINE ESTE FORMULÁRIO DE CONSENTIMENTO INFORMADO A MENOS QUE TENHA TIDO A OPORTUNIDADE DE PERGUNTAR E TER RECEBIDO

RESPOSTAS SATISFATÓRIAS A TODAS AS SUAS PERGUNTAS.

**CONSENTIMENTO INFORMADO**

De acordo com a Declaração de Helsínquia da Associação Médica Mundial e suas atualizações:

1. Declaro ter lido este formulário e aceito de forma voluntária participar neste estudo.
2. Fui devidamente informado(a) da natureza, objetivos, riscos, duração provável do estudo, bem como do que é esperado da minha parte.
3. Tive a oportunidade de fazer perguntas sobre o estudo e percebi as respostas e as informações que me foram dadas. A qualquer momento posso fazer mais perguntas ao médico responsável do estudo. Durante o estudo e sempre que quiser, posso receber informação sobre o seu desenvolvimento. O médico responsável dará toda a informação importante que surja durante o estudo que possa alterar a minha vontade de continuar a participar.
4. Aceito que utilizem a informação relativa à minha história clínica e os meus tratamentos no estrito respeito do segredo médico e anonimato. Os meus dados serão mantidos estritamente confidenciais. Autorizo a consulta dos meus dados apenas por pessoas designadas pelo promotor e por representantes das autoridades reguladoras.
5. Aceito seguir todas as instruções que me forem dadas durante o estudo. Aceito em colaborar com o médico e informá-lo(a) imediatamente das alterações do meu estado de saúde e bem-estar e de todos os sintomas inesperados e não usuais que ocorram.
6. Autorizo o uso dos resultados do estudo para fins exclusivamente científicos e, em particular, aceito que esses resultados sejam divulgados às autoridades sanitárias competentes.
7. Aceito que os dados gerados durante o estudo sejam informatizados pelo promotor ou outrem por si designado.
8. Posso exercer o meu direito de retificação e/ou oposição Tenho conhecimento que sou livre de desistir do estudo a qualquer momento, sem ter de justificar a minha decisão e sem comprometer a qualidade dos meus cuidados médicos. Tenho conhecimento que o médico tem o direito de decidir sobre a minha saída prematura do estudo e que me informará da causa da mesma.
9. Fui informado que o estudo pode ser interrompido por decisão do investigador, do promotor ou das autoridades reguladoras.

***Nome do Participante*** _____

***Assinatura :*** _____

***Data:*** _____/_____/____

***Nome de Testemunha(s) Representante(s)Legal(is):*** _____

_____

_____

***Assinatura:*** _____

***Data:*** _____/_____/____

***Assinatura:*** _____

***Data:*** _____/_____/____

Confirmo que expliquei ao participante acima mencionado a natureza, os objetivos e os potenciais riscos do estudo acima mencionado.

***Nome do Investigador:*** _____

***Assinatura:*** _____

***Data:*** _____/_____/____

## Appendix 2 Article submission and journal instructions

An article based on this study was submitted to *Early Intervention in Psychiatry*.

Early Intervention Psychiatry


**Recovery in First-Episode Psychosis: a network analysis of clinical and personal recovery, antipsychotic adherence and recovery support**

| | |
|---|---|
| Journal: | *Early Intervention in Psychiatry* |
| Manuscript ID | Draft |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Branco, Elisabete; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine<br>Santos, Vítor; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Madeira, Nuno; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Bajouco, Miguel; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Morais, Sofia; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Caldeira, Salomé; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Costa, Helder; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Martins, Maria; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department<br>Macedo, António; Universidade de Coimbra Faculdade de Medicina, Institute of Psychological Medicine; Centro Hospitalar e Universitário de Coimbra EPE, Psychiatry Department |
| Keywords: | First-episode psychosis, Recovery, Network analysis, Early intervention |

As such, this paper was written accordingly to the journal instructions:

**"PREPARING THE SUBMISSION**

**Wiley Author Resources**

*Manuscript Preparation Tips:* Wiley has a range of resources for authors preparing manuscripts for submission available here. In particular, authors may benefit from referring to Wiley's best practice tips on Writing for Search Engine Optimization.

*Article Preparation Support:* Wiley Editing Services offers expert help with English Language Editing, as well as translation, manuscript formatting, figure illustration, figure formatting, and graphical abstract design – so you can submit your manuscript with confidence. Also, check out our resources for Preparing Your Article for general guidance about writing and preparing your manuscript.

**Style**

**Spelling.** The journal uses UK spelling and authors should therefore follow the latest edition of the Concise Oxford Dictionary.

**Units.** All measurements must be given in SI or SI-derived units. Please go to the Bureau International des Poids et Mesures (BIPM) website at http://www.bipm.fr for more information about SI units.

**Abbreviations.** Abbreviations should be used sparingly – only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

**Trade names.** Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name, and the name and location of the manufacturer, in parentheses.

**Parts of the Manuscript**

The text file should be presented in the following order:

i. A short informative title that contains the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips);
ii. A short running title of less than 40 characters;
iii. The full names of the authors;
iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
v. Abstract and keywords;
vi. Main text;
vii. Acknowledgements;
viii. Conflict of interest statement;
ix. References;
x. Tables (each table complete with title and footnotes);
xi. Figure legends;
xii. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

**Authorship**

Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

**Abstract and key words**

All articles must have a structured abstract that states in 250 words (150 words for Brief Reports) or fewer the purpose, basic procedures, main findings and principal conclusions of the study. Divide the abstract with the headings: Aim, Methods, Results, Conclusions. The abstract should not contain abbreviations or references.

Five key words, for the purposes of indexing, should be supplied below the abstract, in alphabetical order, and should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at http://www.nlm.nih.gov/mesh/meshhome.html.

**Text**

Authors should use the following subheadings to divide the sections of their manuscript: Introduction, Methods, Results and Discussion.

**Acknowledgments**

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

**Conflict of Interest Statement**

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section 'Conflict of Interest' in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

**References**

References should be prepared according to the Publication Manual of the American Psychological Association (6th edition). This means in text citations should follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper.

A sample of the most common entries in reference lists appears below. Note that for journal articles, issue numbers are not included unless each issue in the volume begins with page one, and a DOI should be provided for all references where available.

*Journal article*

Beers, S. R., & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *The American Journal of Psychiatry*, *159*, 483–486. doi:10.1176/appi.ajp.159.3.483

*Book*

Bradley-Johnson, S. (1994). *Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school* (2nd ed.). Austin, TX: Pro-ed.

*Internet Document*

Norton, R. (2006, November 4). How to train a cat to operate a light switch [Video file]. Retrieved from http://www.youtube.com/watch?v=Vja83KLQXZs

**Tables**

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

**Figure Legends**

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

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Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

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