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Preliminary title:

A comparative network analysis of a compiled UHR cohort using CAARMS scores.

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Working and writing group:

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Work Packages involved: WP5, WP7

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: VU University Amsterdam (M. van der Gaag)

Objectives (scientific background, hypothesis, methods, and expected results):

Scientific background

The last decennia there have been great advancements in the area of detection and treatment of an increased risk of developing a first psychotic episode.(van der Gaag et al., 2013) By combining biological, psychological and social characteristics sensitivity or specificity of prediction of transition to psychosis can be increased. (Fusar-poli et al., 2017) Treatment with Cognitive Behavioral Therapy results in a lower transition rate to psychosis and an increased level of wellbeing (Rietdijk et al., 2010)(Morrison et al., 2012). However, identification of those most at risk is still insufficiently robust. More sensitive and specific predictors and targets for intervention could assist further advancements in this area.

In concordance with trends in psychopathological classification in general, questions have also risen about the legitimacy of a categorical view of UHR. (Kendler, Zachar, & Craver, 2017)(Os & Linscott, 2012) The categorical divisions are especially questionable in early stages, where symptoms haven't developed into syndromes yet. In this fashion, it has been suggested that targeting symptoms is important regardless of the likelihood of transition. (Ruhrmann, Schultze-Lutter, & Klosterkötter, 2010) (McGorry & Nelson, 2016) (Wigman, de Vos, Wichers, van Os, & Bartels-Velthuis, 2016)

Recently a new approach to evaluate psychopathological symptoms has been developed: network analyses. This form of analysis may be a superior way to evaluate symptom structures and circumvent the problem of increasing number of categories (Borsboom & Cramer, 2013; Goekoop & Goekoop, 2014). Network theory enables empirically justified modeling in a non-linear way. As such, it enables going beyond the level of syndromes and focus trans-diagnostically on the role of individual symptoms and their interaction (Fried et al., 2016; Wigman et al., 2015). Contrary to latent class analysis the network structure does not rely on the assumption of latent factors or common causes, to unite symptoms into syndromes (i.e. clusters). Clusters can also emerge and persist as a consequence of

mutual reinforcement of symptoms themselves. Furthermore, very recent work has experimented with a hybrid system of LCA and network analysis. This hybrid system combines both the common cause model of LCA and the mutual reinforcement model of network analysis. (Golino & Epskamp, 2016)

The nature of network analysis makes it possible to gain insight into the underlying structure of psychopathology by showing association between symptoms. This can generate hypotheses about interaction between symptoms, guiding future time-series research into actual causality. At the level of structure, networks of different groups can be compared and specific characteristics of networks may predict the risk of transition to a psychotic disorder. (Fried, Cramer, Boschloo, & Borsboom, 2016) Furthermore, network analysis can be used to model dynamics and be a common language between the neurobiological, clinical and social level (Looijestijn, Blom, Aleman, Hoek, & Goekoop, 2015; Scheffer et al., 2009)

The Comprehensive Assessment of At Risk Mental State (CAARMS) is a reliable and valid measure to identify individuals at Ultra High Risk (UHR) to develop a psychotic disorder. (Yung et al., 2006) Studies have mapped the structure of CAARMS by looking at the individual items of this questionnaire. (Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012) (Raballo, Nelson, Thompson, & Yung, 2011) In these studies the symptoms of UHR were divided into different dimensions. These studies used PCA as the tool to reduce data; explaining a substantial part of the total variance in terms of a smaller amount of principal components.

By using this method of data reduction it is assumed that individual symptoms are explained by one principal component (i.e., symptoms belong to one category only). In that sense, breaking the category UHR down into dimensions through PCA, is not actually dimensional but in line with the categorical view of psychopathology that DSM holds. In network analysis, on the other hand, symptoms can belong to different clusters. The upside of PCA is heuristic clarity, the downside of the a-priori exclusion of the possibility that a symptom can belong to different categories, is a loss of information. Within the network approach this information is not lost and this may better reflect the nature of the dimensional structure of psychopathology.(Boschloo, Schoevers, Van Borkulo, Borsboom, & Oldehinkel, 2016)

However, limitations of network theory should also be acknowledged. It is a relatively new field and questions regarding the stability and generalizability of networks need evaluation. The large amount of (conditionally independent) relations within a network, make it difficult to gain enough power. Therefore methods of regularization are needed and increasingly considered.(Epskamp, Kruis, & Marsman, 2016)

In summary. Prediction of transition is needed and further mapping of UHR symptoms could guide hypothesis and interventions. Research has been done to map UHR symptoms but the method of PCA loses information. Recent advancements in network analysis may be able to attribute to both prediction of transition and mapping the UHR group.

Key goals

1. Identifying key symptoms and their interactions in a network structure of baseline CAARMS symptoms.

2. Make a comparison on the level of network structure between the group UHR that made transition to psychosis and those that did not. Are networks structures of UHR-NT and UHR-T groups significantly different?

We expect that symptom patterns in UHR individuals may generate hypothesis for further time-series research and possible treatment.

We hypothesize that there is a significant difference in network structure between UHR-T and UHR-NT groups in terms of connectivity between symptoms.

Expected results

We expect to be able to make sufficiently stable and accurate networks to make 1) robust comparison between different network measurements and 2) comparison between network structures of UHR-T and UHT-NT groups.

Methods

In order to generate enough power, different UHR cohorts need to be combined. The aim is to combine baseline CAARMS data and transition data from the EDIE-NL, EU-GEI and NEURAPRO study groups to compose a cohort of n=714 UHR individuals (UHR-NT: n=619; UHR-T: n= 95).

This data will be used for 1) generating networks of UHR-T and UHR-NT groups on T0, 12 and 24 months, 2) analysing the networks and 3) comparing networks of UHR-T and UHR-NT groups.

Baseline ARMS and FEP data needed for the study:

- CAARMS data on T0, 12 months and 24 months -> WP5, WP7
- Transition data → WP5

Plan for statistical analysis (overall strategy):

PCA (with Scree plots and Horn's parallel analysis) will give a first mapping of the data and enables comparison of the compiled cohort to previous studies.

To compute and analyze networks, we will use R Studio and different packages developed for network analysis. First, the combined data will be used to generate a variance co-variance matrix, calculating conditionally independent relations. Significance calculations (with Bonferroni correction for multiple testing) cannot be used at this level because this would necessitate cohort sizes that are not realistic in psychiatric research. Hence, in order to make a model and level up the signal to noise ratio, LASSO (least absolute shrinkage and selection operator) regularization will be used. LASSO makes use of a hyper-parameter λ. The value of λ will be chosen using EBIC (Extended Bayesian Information Criterion) in order to find the 'sweet spot' between parsimony and goodness of fit. (Epskamp, 2016)

The accuracy and stability of the network itself and analysis of the network, will be investigated using tho different methods. The accuracy can be tested using non-parametric bootstrap resampling. This method tests sampling variability in edge-weights and wether edge weights and and centrality indices (betweenness, closeness and strength) significantly differ form each other. The accuracy will be expressed in 95% confidence intervals. Stability of centrality will be tested using the case dropping subset bootstrap method on the centrality indices. (Epskamp, Borsboom, & Fried, 2016)

Comparison of the structure of different networks (UHR-T and UHR-NT) can be done using the package NetworkComparisonTest. This package applies permutation based hypothesis test on network structure invariance, global strength invariance and edge invariance.(van Borkulo et al., 2015)

The graphical representation of the network will be generated using the package q graph. Using a 'spring' model groups the items in terms of strength of association; clustering certain symptoms. Superimposing on this graphical representation the PCA clusters, makes it possible to inspect the relation between PCA - and network cluster

Other analyses/methods:

N/A

Involvement of external Parties (non EU-GEI): AMC medical centre VU medical centre
IPR check:
Timeframe: Month 1: Literature search; obtaining, merging, checking, cleaning of data Month 2: Completion of statistical analysis and first draft of manuscript Month 3: Manuscript submission
Additional comments: N/A