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Quantitative and qualitative symptomatic differences in individuals at Ultra-High Risk for psychosis and healthy controls

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ABSTRACT

Patients at Ultra-High Risk (UHR) for developing a first psychosis vary widely in their symptom presentation and illness course. An important aim in UHR research concerns the characterization of the clinical heterogeneity in this population. We aimed to identify qualitatively and quantitatively different clinical symptom profiles at baseline and at 2-year follow-up in a group of UHR subjects and healthy controls. We employed a Latent Class Factor Analysis (LCFA) to the 19 items of the Structured Interview for Prodromal Syndromes (SIPS) ratings at baseline and at 2-year follow-up in a sample of 147 UHR subjects and 141 controls from the Dutch Prediction of Psychosis Study (DUPS) in the Netherlands. Additionally, a stepwise logistic regression analysis was performed with transition to psychosis as a dependent variable and baseline latent variable scores as predictors. Variation in symptomatology at baseline was explained by both quantitative and qualitative differences; at 2-year follow-up qualitative differences between individuals were no longer observed. Quantitative differences showed moderate stability over time (range=0.109–0.42). Within the UHR sample, transition to psychosis was significantly associated with quantitative differences in baseline SIPS scores. The results of our study suggest a 'quasi'-continuous extended psychosis phenotype, a finding that merits replication in other samples.

1. Introduction

The introduction of the Ultra-High Risk (UHR) concept (Yung et al., 1996) has instigated a great leap forward in the identification of individuals at risk of developing a first psychosis. Young help-seeking people meeting at least one of the UHR criteria have, on average, a 29% risk of developing psychosis in the 31 months following first clinical presentation (Fusar-Poli et al., 2012). Nevertheless, possibly due to quicker referral as a consequence of growing awareness among clinicians, in more recent studies lower transition rates are being reported (e.g. Ruhrmann et al., 2010; Yung et al., 2008; Simon et al., 2011; Ziermans et al., 2011), and most of the studies primarily emphasizing the additional predictive value of single risk factors lack consistent replication (Thompson et al., 2010). The vast majority of people who meet UHR criteria do not develop a psychotic disorder. Individuals at UHR for developing a first psychosis can vary widely with respect to their overall symptom presentation and illness course. While a significant proportion of those seeking help for UHR symptoms will remit from their symptoms within a year, others will still report similar symptoms at 2-year follow-up, show transition to psychosis or will develop other psychiatric disorders (Insel, 2010; Addington et al., 2011; Simon et al., 2010; Velthorst et al., 2011; Ziermans et al., 2011). Therefore, an important aim in the study of UHR individuals concerns the characterization of the large clinical heterogeneity in this population.

In a study addressing the clinical diversity of UHR populations, Demjaha and colleagues recently employed a factor analysis (FA), aiming to explore the different psychopathological dimensions within 122 UHR individuals. Instead of focusing on which individual symptom would predict transition best, they examined whether young people with high loadings on a certain constellation of symptoms were at a particularly high risk for transition to a

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first psychotic episode. Their results indicated that higher loadings on the disorganization/cognitive dimension were associated with an increased risk of developing a first psychosis within 24 months (Demjaha et al., 2010).

Factor analysis identifies underlying (i.e. latent) constructs and employing this method in a UHR sample is a laudable step towards the identification of more homogeneous subgroups in the heterogeneous UHR cohorts. However, although traditional factor analysis offers a great opportunity for such a data reduction, it requires all latent factors to be continuous. An alternative approach is Latent Class Analysis (LCA) that was developed for the identification of categorically different subgroups (i.e., categorical latent factors). Thus, while factor analysis is based on the assumption that variation in a population is due to continuous differences between subjects, LCA allows for categorical differences. It is not unlikely that variation in a population is in reality explained by both continuous and categorical differences. For example, we could speculate that UHR and control subjects form categorically different subgroups in a population while differences within these groups are mainly due to differences in severity. The latent structure of psychological constructs can be investigated with a wide variety of models which range from strictly dimensional approaches (i.e., factor analysis) to strictly categorical approaches (i.e., Latent Class Analysis). Masyn et al. (2010) developed a conceptual framework for these models. In the current study, we have chosen a type of model that allows for categorically different subgroups (e.g., controls vs. UHR or UHR subjects with transition to psychosis vs. UHR subjects with no transition to psychosis) and for severity differences within a population. We assumed that the measurement model of the continuous factors is similar in the different latent classes. The use of a combined latent class and factor analytical (LCFA) approach can help to clarify whether categorical or continuum models are more informative and whether a certain symptom profile indicates a worse disease outcome. This approach is recently applied to psychotic patients their relatives and healthy controls (Derks et al., 2012).

In the current 2-year follow-up study we employed a similar analysis, using combined latent class and factor analysis in a relatively large sample of patients at UHR for developing a first psychosis and a group of healthy controls. Examining symptom constellations in UHR research may contribute to the early recognition of individuals that are at imminent risk for developing a first psychosis, may inform specific treatment-needs and may add to a more valid assessment of the prodromal phase of schizophrenia.

Specifically, our study aims were to (i) identify qualitatively and quantitatively different clinical symptom profiles in a group of UHR subjects and healthy controls based on 19 items of the Structured Interview for Prodromal Syndromes (SIPS); (ii) examine whether such symptom profiles are stable over time and; (iii) determine whether a certain constellation of symptoms is particularly related to transition to a first psychotic episode.

2. Methods

2.1. Design

This prospective study, with a naturalistic design, is part of the longitudinal Dutch Prediction of Psychosis Study (DUPS) that was performed at University Medical Center Utrecht and the Academic Medical Center Amsterdam which are both situated in the Netherlands. Informed consent was obtained before inclusion. Individuals younger than 18 years of age signed for assent, while their parents signed for informed consent. Individuals aged 18 years or older signed for informed consent themselves.

2.2. Recruitment of subjects

The total sample consisted of 289 individuals, of whom 148 subjects were at Ultra-High Risk (UHR) for psychosis while the remaining 141 subjects were healthy controls. All UHR individuals were referred to the study by general practitioners or psychiatric clinics. UHR status was defined by meeting at least one of the four criteria for UHR at baseline (Velthorst et al., 2009) and are similar to frequently used criteria for UHR. Briefly, the first three inclusion criteria were assessed using the semi-structured interview, Structured Interview for Prodromal Syndromes and require the presence of one of the following (SIPS, Miller et al., 2002): (1) attenuated positive symptoms (APS); (2) brief, limited, or intermittent psychotic symptoms (BLIPS; a brief psychotic episode of less than 1 week's duration that spontaneously remits without antipsychotic medication); (3) a 30% reduction in overall level of social, occupational/school, and psychological functioning (i.e., global assessment of functioning [GAF; American Psychiatric Association, 1994]) in the past year, combined with a genetic risk of psychosis. The fourth inclusion criterion, Cognitive Disturbances (COGDIS) was assessed using the Bonn Scale for the Assessment of Basic Symptoms—Prediction List (Klosterkötter et al., 1996) (BSABS—P): (4) two or more of a selection of nine basic symptoms, such as subjective deficits in cognitive, perceptual, and motor functioning. Healthy controls were mostly recruited from secondary and high schools.

Controls were excluded if they met one of the UHR criteria, if they or a first-degree relative had a history of a psychiatric disorder, or if they had a second-degree relative with a psychotic disorder. Exclusion criteria were assessed using SIPS and BSABS—P interviews and (parent) questionnaires. Additionally, both control and UHR individuals were excluded if there was evidence for any past or present neurological disorder (e.g., epilepsy), drug or alcohol abuse.

2.3. Transition to psychosis

A transition to psychosis was defined as a continuation of BLIPS, i.e., as one or more psychotic symptoms persisted for more than 7 days. At the Academic Medical Center, Amsterdam, this was validated by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and was defined as 'having a score of four or more on hallucinations, delusions or formal thought disorder'. At the University Medical Center, Utrecht, the psychosis threshold was determined with the SIPS-Positive Symptoms subscales. Transition was defined as 'having a score of 6 on any of the items of the SIPS-Positive Symptoms subscales for a period of more than 7 days' (Cannon et al., 2008; Ruhrmann et al., 2010). Chart reviews were used to retrospectively confirm psychotic transition by clinical consensus. The six interviewers (DHN, TZ, and four other trained psychologists) received a 2-day training workshop by Dr. T.J. Miller, one of the SIPS authors, including a reliability check after approximately 6 months. The pairwise inter-rater concordance of the SIPS was 77% in Amsterdam and 89% in Utrecht.

In both research centers, psychotic subjects were subsequently diagnosed according to the DSM-IV guidelines to establish a formal diagnosis (American Psychiatric Association, 1994).

2.4. Instruments

2.4.1. The Structured Interview for Prodromal Symptoms (SIPS)

The SIPS (Miller et al., 2002), was used to determine the presence, severity and type of prodromal symptoms. The Scale Of Prodromal Symptoms (SOPS), the rating scale of the SIPS, has four SIPS subscales that include five Positive Symptom items, six Negative Symptom items, four Disorganization Symptoms items and four General Symptom items. All symptoms are rated on a 7 point rating scale rating from 0 (Never, absent) to 6 (Severe/Extreme and Psychotic for the positive items). The diagnosis of a prodromal state is based on the score at the positive items. Scores in the 3–5 range are considered as indicative of the UHR phase (APS). A score of six signifies psychosis or BLIPS (Miller et al., 2002). To prevent statistical bias due to low frequencies in some of the answer categories, the items were recoded in such a way that each category included at least 5% of the participants (see Supplementary Table S1). For example, the item "Unusual thought content/delusional ideas" was present to some extent in the majority of the subjects and only the two most extreme categories (severe but not psychotic and severe and psychotic; 13.9% of the participants) were combined. In contrast, the item "disorganized communication" was absent in the majority of the individuals and the four highest categories (moderate to severe and psychotic; 9% of the participants) were combined.

2.5. Statistical analyses

Model fitting was performed on 19 SIPS symptoms at baseline and follow-up separately. The model that was fitted to the data allows for both dimensional and categorical latent variables. While the model is a combination of factor analysis and Latent Class Analysis we will first briefly explain these concepts and will then describe the combined model. In factor analysis (FA) differences in observed scores are explained by one or more continuous latent factors. The observed scores are associated with the latent factors through factor loadings (the factor weights). The variation in observed items that is not explained by the latent factors is contributed to by measurement error. In Latent Class Analysis (LCA; McGutcheon, 1987) categorical latent variables are used to identify homogeneous groups of individuals. Variation in observed item scores is explained by a categorical latent variable.