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Prodromal symptoms and remission following first episode psychosis

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ABSTRACT

Introduction: Describing the trajectory of prodromal symptoms has obvious appeal in supporting advances towards sub-clinical intervention. Identifying clinical phenomena associated with unfavourable illness outcomes could have greater significance in explaining some heterogeneity within and between psychotic disorders and advancing understanding of pre-psychotic typologies. Few studies have assessed the continuity, if any, between prodromal phases and illness outcome one year after treatment.
Methods: We assessed 375 people with first-episode psychosis (FEP) and 215 (57.4%) were seen approximately one year later. We performed factor analysis on prodromal symptom items obtained by interview with families and participants and identified a five-factor solution. We determined whether these factors predicted non-remission from psychosis in the presence of other factors that may predict outcome including premorbid adjustment, duration of prodrome and untreated psychosis (DUP), baseline symptoms and DSM-IV diagnoses. We used random forest classification to predict the most important variables and logistic regression to identify specific predictors.
Results: We identified five prodromal symptom factors comprising Negative Symptoms, General Psychopathology, Reality Distortion, Strange Ideas and Irritability. Prodromal symptoms did not predict a greater risk of non-remission with the exception of Irritability and this factor was also associated with earlier age at onset, being male and a diagnosis of substance-induced psychosis. Being male, DUP and baseline positive symptoms predicted non-remission at one year.
Conclusion: Prodromal symptoms were not linked with outcome after a year of treatment which could be explained by greater heterogeneity in illness psychopathology which may be more pronounced in broad FEP diagnoses at different stages. It could also be explained by prodromal symptoms exerting greater influence earlier in the course illness.

1. Introduction

The characteristic features of the prodrome are largely non-specific psychological, emotional and behavioural changes temporally related to the onset of a psychotic illness (Hambrecht et al., 1994; Hafner et al., 1992). Prodromal durations can span a few days to several years (Lyne et al., 2014; Clarke et al., 2006; Keshavan et al., 2003; Häfner et al., 2003) with the most frequently occurring symptoms comprising both subjective and observable signs of attenuated psychosis including suspiciousness and social withdrawal and deterioration in role functioning. Alongside this, general psychopathological symptoms are frequent including depression, anxiety and sleep disturbance (Hafner et al., 1992; Iyer et al., 2008; Norman et al., 2005a; Beiser et al., 1993). While the pattern and course of these symptoms are still uncertain (Häfner et al., 2003; Yung and McGorry, 1996; Schultze-Lutter et al., 2010), there is a remarkable degree of similarity between the frequency and type of signs and symptoms that occur during this phase (Iyer et al., 2008; Yung and McGorry, 1996).

Describing the trajectory of emergent symptoms has obvious appeal in supporting advances towards subclinical intervention (Yung et al., 2003). Few studies however, have attempted to classify these symptoms and determine their influence on outcome following treatment to assess continuity between subclinical symptoms and frank psychotic illness. Examining these possible links could help clarify some issues

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regarding heterogeneity within and between psychosis diagnoses and further advance the typology of psychotic disorders (Larson et al., 2010; Gourzis et al., 2002). Recent studies of first episodes, of which there are few, have focused primarily on establishing if prodromal symptoms are associated with symptoms, diagnosis and functioning at presentation and after one year (Lyne et al., 2014; Iyer et al., 2008; Norman et al., 2005a). The findings are inconsistent with one study showing a link between prodromal psychobiological changes and positive symptoms at one year (Norman et al., 2005a) and no association in another (Häfner et al., 1999). Equally, continuity between negative symptoms has been demonstrated at baseline but not following treatment (Lyne et al., 2014; Norman et al., 2005b).

Given the interest in identifying clinical phenomena associated with unfavourable illness outcomes or even chronicity we sought to examine the possible significance of prodromal symptom patterns for later outcome. Using symptom-based, standardised criteria we aimed to establish whether the likelihood of achieving remission status at one year was influenced by the presence of prodromal symptoms and if so, which types. Specifically, we hypothesised that the prodromal symptoms that we considered coterminous with fully-fledged psychotic symptoms would be correlated, namely positive and negative symptoms. Longer duration of untreated illness is also a risk factor for non-remission (Clarke et al., 2006) and as we propose that prodromal duration and symptoms are important in predicting outcome we included these in the analysis alongside variables typically related to outcome. We therefore aimed to establish whether there were differences between the type of prodromal symptom and prodromal duration and whether either of these increased the risk of non-remission.

2. Methods

2.1. Study participants & setting

Participants included consecutive in-patient and community admissions aged 16 to 65, to an Early Intervention in Psychosis Service (EIS) covering a geographically defined catchment area (population approx. 390,000) in Dublin and the mid-Leinster region of Ireland. First presentations with psychosis to three publicly funded community mental health services and one private inpatient psychiatric hospital between February 2005 and April 2011 were included. Participants were excluded if they were not experiencing FEP (defined as no previous episodes treated with antipsychotic medication more than thirty days), had a known learning difficulty (IQ < 70) or psychosis due to a general medical condition.

2.2. Measures and procedures

Assessments typically commenced within 72 h of receipt of referral from clinical teams and were complete within 2–4 weeks at inception into the study (baseline) and approximately one year later (follow-up). Consequently few participants had received adequate trials of antipsychotics. An emphasis on referral of suspected FEP cases identified two non-cases for every case (O'Donoghue et al., 2012). At both time points, diagnoses were obtained using the Structured Clinical Interview for DSM IV (SCID) (First et al., 1995). We assessed symptoms using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Calgary Depression Scale (Addington et al., 1993). We determined global functioning using the Global Assessment of Functioning Scale (GAF). These scales have demonstrated good psychometric properties including reliability, internal consistency and predictive validity (Andreasen, 1984; Andreasen, 1983; Addington et al., 1993; Andreasen et al., 1995; Collins et al., 1996; Startup et al., 2002). Premorbid adjustment was established using the modified Premorbid Adjustment Scale (van Mastrigt and Addington, 2002). The total score was calculated by averaging the scores of all time periods (childhood, early adolescence, late adolescence and adulthood) excluding items from developmental stages which occurred subsequent to the onset of the psychosis prodrome. Remission of positive and negative symptoms was determined using the Remission in Schizophrenia Working Group (RSWG) (Andreasen et al., 2005) criteria in the month preceding assessment.

Pre-treatment symptom frequencies were derived from interviews with families/carers using the Onset Questionnaire (Beiser et al., 1993) and augmented by participant interview. The initial stage assessed is first noticeable signs (FNS) and contains 30 binary items in four higher order categories including attitude/thinking, mood, behaviour and performance and somatic signs. Estimates of the DUP, DUI and duration of prodrome (DP) are also provided and good reliability has been demonstrated in determining these. As the scale development did not report on the internal consistency of symptom patterns we performed principal component analysis to determine the underlying factor structure of the 30 prodromal symptoms in the FNS described above.

DUP was defined as the interval between the first psychotic symptom and the initiation of the first assessment for treatment. Participants whose prior treatment timeline did not clearly meet the criteria for FEP were included if they had no more than 30 days prior antipsychotic treatment for a psychotic disorder. DP was defined as the interval between the onset of the FNS and the onset of psychosis and DUI estimates comprised both DP and DUP. Consensus was obtained on both FEP caseness, DUP and DUI at weekly meetings chaired by the Department Head. Clinical assessors (post-membership registrars and clinical nurse specialists) received comprehensive training and inter-observer agreement was tested on between 5 and 10 cases. Concordance on diagnoses was observed in 90% of cases. Intraclass correlations for the SANS (.67–.99), SAPS (>.87), CDSS, PAS and GAF (>.95) and DP and DUP (>.85) were acceptable. Ethical approval was granted by each organisation's ethics committee.

2.3. Statistical analysis

Analyses were conducted using both SPSS 22 and R 3.1.0 (R Development Core Team, 2010; IBM Corporation, 2013). These data were examined for compliance with the statistical assumptions of multivariable analysis. DUP, DUI and DP were all highly positively skewed and log10 transformed. Baseline symptom measures were normally distributed except depression (CDSS) and the square root of raw scores was calculated. Chi-square tests and independent sample t-tests were used to investigate any potential sources of bias caused by differences between follow-up completers and non-completers. The same tests were used to examine differences between remission statuses. There were fewer data on DP (n = 323) than DUP (n = 348). We performed a principal component analysis (PCA) on the 30 FNS items contained in the Onset Questionnaire producing a component matrix of inter-correlated items and after exploring various rotations a five-factor solution denoting prodromal onset symptoms was obtained. We used independent t-tests to determine differences in prodromal symptom factors and diagnosis, DP and DUP estimates with back-transformed means per group to facilitate clinical interpretation. Welch's coefficient was reported where Levene's test indicated non-normal variance between groups tested. For skewed data, a one unit perturbation with log10 transformation led to approximately normal distributions.

We then performed a two-step procedure to investigate the contribution of candidate explanatory variables to non-remission (remission = 0, non-remission = 1). Multicollinearity and model over-specification are specific concerns so we conducted random forest (RF) classification analysis. RF classification can robustly estimate parameters by repeated simulation on "training" subsets of the data (67%) to grow the "forest," which are then assessed on a separate "test" subset of the data (33%). The sample selection is randomly repeated for different sizes of forests, until stability of the prediction rate is achieved. Classifications trees were used to predict the target variable (e.g., non-remission) based on

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