Expressed Emotion as a Predictor of the First Psychotic Episode - Results of the European Prediction of Psychosis Study

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Abstract

Objective: To investigate the impact of expressed emotion (EE) on the risk of developing the first psychotic episode (FEP).

Method: The European Prediction of Psychosis Study (EPOS) investigated 245 patients who were at clinical high risk (CHR) of psychosis. The predictive value of EE alone and as a part of the multivariate EPOS model was evaluated.
**Results:** 'Perceived irritability', a domain of the Level of Expressed Emotion Scale (LEE), was found to be predictive for the First Psychotic Episode (FEP), even as an individual variable. Furthermore, it was selected in the multivariate EPOS prediction model, thereby replacing two of the original predictor variables. This led to an improved revised version that enabled the identification of three significantly different risk classes with a hazard rate of up to 0.911.

**Conclusions:** CHR subjects who perceive the most important person in their individual social environment to be limited in their stress coping skills had a higher risk of conversion to the first psychotic episode. The importance of this risk factor was further demonstrated by an improvement of risk estimation in the original EPOS predictor model. Perceiving a reference person as stress-prone and thus potentially unreliable might amplify self-experienced uncertainty and anxiety, which are often associated with the prodromal phase. Such an enforcement of stress-related processes could promote a conversion to psychosis.

**Keywords:** Level of Expressed Emotions (LEE) Scale; First Psychotic Episode (FEP); COGDIS; ultra-high risk; prediction
1. Introduction

The psychological construct of expressed emotion (EE) was originally developed as a measure of the emotional attitude and the communication style of caregivers towards mentally ill people (Brown, 1966; Brown et al., 1972). EE has been shown to be a reliable and valid predictor of adverse clinical outcomes for a range of different mental disorders (Butzlaff and Hooley, 1998; Leff et al., 1985; Miklowitz, 1987; Priebe et al., 1989), including the relapse of psychosis (Bebbington and Kuipers, 1994; Brown et al., 1972; Butzlaff and Hooley, 1998; Hooley, 2007; Onwumere et al., 2009; Phillips et al., 2007; Vaughn and Leff, 1976). In the families of First Episode Psychosis (FEP) patients, the prevalence rates of high EE ranged from 32 to 73.5 percent (Heikkila et al., 2002; McNab et al., 2007; Meneghelli et al., 2011; Onwumere et al., 2009; Raune et al., 2004). Increased levels of EE were even recorded in subjects who experienced symptoms that are associated with a clinical high risk state (CHR) of developing a psychotic disorder (Meneghelli et al., 2011; Schlosser et al., 2010; Tsai et al., 2015). CHR is defined by either basic symptom (BS) criteria (Schultze-Lutter, 2009) and/or ultra-high risk (UHR) criteria (Schultze-Lutter et al., 2013). Two UHR studies, using the Structured Interview for Psychosis-Risk Syndromes (SIPS), reported a positive correlation of criticism levels with positive symptom severity during the 6-month follow-up (Schlosser et al., 2010) or a negative correlation with the severity of negative symptoms at the baseline, respectively (Tsai et al., 2015). However, one study, using the Brief Psychiatric Rating Scale, found no correlation of increased EE levels with symptom severity in a UHR sample (Meneghelli et al., 2011). A 15-year family study following non-psychotic adolescents with behavioural difficulties suggested that EE increased the risk for FEP (Goldstein, 1987). Furthermore, a risk increasing gene × EE interaction was observed in the offspring of mothers with schizophrenia (Tienari et al., 2004).

In contrast to the relationship between EE and relapse in already clinically manifest psychotic disorders, the impact of EE on conversion into the first psychotic episode in subjects clinically at a high risk still has to be explored.

EE has been assessed in various ways. The semi-structured Camberwell Family Interview (CFI) (Vaughn and Leff, 1976) has been conducted with key relatives to analyse the quality of communication between index patients and their significant others. As the CFI is rather time-consuming, alternatives have been developed for use in larger samples (Hooley and Parker, 2006). The Five Minute Speech Sample (FMSS) (Magana et al., 1986), for instance, allows family members to voice their thoughts and feelings for five minutes; the recording is later coded for the overall level of EE and criticism. While these instruments focus on the perspectives of the relatives, the Level of Expressed Emotion Scale (LEE) (Cole and Kazarian, 1988) is a valid, feasible, and economic measure of EE with good psychometric properties (Gerlsma and Hale, 1997), which provides the opportunity to assess the experiences of patients in their social environments.

1.1. Aims of the study

As part of the European Prediction of Psychosis Study (EPOS), a prospective, naturalistic field study, we aimed to investigate the relationship between the EE perceived by the CHR patients and the risk of conversion to psychosis. EPOS developed a six-factor prediction model and introduced risk stratification by a
prognostic index in the CHR research (Ruhrmann et al., 2010). We examined the following hypotheses: (1) the perception of EE is predictive for conversion to psychosis and (2) introducing the EE variables will improve the EPOS prediction model.

2. Method

2.1 Participants

After approval by the respective local ethic committees, 245 CHR participants were recruited from early-detection services at six European University centres (consort chart Figure S1). Written informed consent was obtained from all the participants (or their parents if they were minors). Aside from an age range of 16–35 years, the inclusion criteria comprised a CHR syndrome defined by the BS criterion 'cognitive disturbances' (COGDIS) as well as by a modified version of the UHR criteria (Table S1). Exclusion criteria included having experienced a prior psychotic episode for more than seven days according to DSM-IV, having symptoms relevant for inclusion arising from a known general medical disorder, drugs, or alcohol dependency, and a verbal IQ < 85. Conversion was operationalized by the presence of a SIPS positive item with a severity score of six (= psychotic) for more than seven days. EE was assessed in 235 patients (characterized in Table 1). The follow-up period was 18 months. During this period, antipsychotic (AP) drugs were prescribed to 31 (13.2%) patients, antidepressants (AD) to 45 (19.1%) patients, and a combination of both to another 21 (8.9%) patients; no valid information was available for 30 (12.8%) subjects.

2.2 Assessments

Since not only observer assessments (Hooley and Parker, 2006; Magana et al., 1986; Vaughn and Leff, 1976) but also the subjective perception of patients’ EE has been considered an important predictor of relapse (Cole and Kazarian, 1993; Hooley, 2007), the 38-item version of the LEE (Cole and Kazarian, 1988, 1993; Gerlsma and Hale, 1997; Gerlsma et al., 1992) was included in the broad EPOS battery. The four subscales are as follows: perceived lack of emotional support (19 items), perceived intrusiveness (8), perceived irritability (6), and perceived criticism (5). Items are assessed on a four-point Likert scale from 1 = 'untrue' to 4 = 'true' (higher scores imply worse conditions) with regard to the most influential person in the respondents’ lives during the preceding three months.

To the best of our knowledge, this is the first time the LEE was used in a CHR sample. In addition to the already available English and Dutch versions the scale was also translated into German and Finish; further statistical and psychometric details have been reported in Table S2. Cox regressions were controlled for any language effects by considering the ‘centre’ as a potentially confounding variable (Twisk, 2006).

At-risk psychopathology was assessed by the SIPS, version 3.0 (McGlashan, 2001) and by the Bonn Scale for the Assessment of Basis Symptoms (BPAPS-P) (Schultze-Lutter, 2002). The 4 SIPS subscales (positive, negative, disorganization, and general symptoms) include 4–6 items (19 in total) rated on a seven-point severity scale (scores = 0–6). The EPOS investigators, experienced clinical psychologists, and psychiatrists received extensive training by one of the scale’s authors, Tandy J. Miller, PhD. Pairwise inter-rater concordance for the SIPS was 77 percent, which was determined
acceptable by the training team (Ruhrmann et al., 2010). BSABS-P, an abbreviated item list of the Schizophrenia Proneness Instrument (SPI-A) (Schultze-Lutter, 2007), includes three subscales, providing a total of 33 cognitive, perceptual, and motor disturbances assessed on a seven-point severity scale (scores = 0–6), with the maximum frequency of occurrence during the preceding three months as the guiding criterion. Every item corresponds to a single symptom. The BSABS-P differs in structure from the SIPS; in SIPS, items are mostly defined by multiple symptoms. The EPOS investigators received repeated training by one of the scale’s authors, Frauke Schultze-Lutter, PhD. The concordance rate, with expert rating (Frauke Schultze-Lutter), was 87.9 percent (Ruhrmann et al., 2010).

2.3 Statistical Analysis

The predictive value of each individual LEE subscore was calculated separately by univariate Cox regression analyses (CRAs). To identify the most predictive combination, all the LEE scores were then entered into a stepwise CRA.

After testing the stability of the original six-factor EPOS model in a sample with complete LEE and EPOS prognostic score (PS) variables (n = 230, 35 converters), including a bootstrapping procedure (5000 samples) (Loughin, 1998; Tropsha et al., 2003), we explored the impact of the remaining LEE variables on the EPOS PS. Variables with a bootstrapping 95-percent confidence interval, including zero between the lower and the upper bounds were omitted (Loughin, 1998). All the original variables were entered in blockwise CRA; the LEE variables were added stepwise in the second block. The robustness of the resulting model was assessed by a further bootstrapping procedure; after removing two variables, another bootstrapping process was executed. Statistical indices resulting after bootstrapping have been reported. According to Vittinghoff and McCulloch, (2007), five events per predictor were defined as the minimum requirement for the final Cox model. The final regression equation was used to calculate a PS for each participant (Machin et al., 2006). Clinical usability was achieved by stratification into a prognostic index with clinical, or in terms of risk enrichment, as a scientific convenience of the major criterion for stratification (Machin et al., 2006). The other criterion for this explorative stratification process was the significant difference between the risk classes (Tarone–Ware test) (Machin et al., 2006).

The potentially confounding effects of ‘medication and drug abuse’ were tested according to the work of Hosmer and Lemeshow (1999). To control for effects, ‘centre’ was entered as the strata variable (Twisk, 2006). The subjects were considered censored at end of 18 months when the follow-up lasted longer. In accordance with the work of Cannon et al., 2016, the so-called ‘C-index’ was calculated as equivalent to the area under the curve (AUC) of the receiver operating curve (ROC) analysis.

As one of the 19 LEE items of the subscale, the 'perceived lack of emotional support' was missing in the German version ('hears me out'; 35.7 percent of the sample), the median of the individual scores of this subscale was imputed for the respective cases. The correlation of the resulting subscale score of the whole sample with the subscale score resulting after omitting Item 15 from the database was $r = 0.998$. Furthermore, neither results of the univariate nor the multivariate Cox regression analyses differed. Thus, we decided to report the results obtained with imputed scores.
For group comparisons not including survival times, we used the Mann–Whitney test, the chi² test, and the Fisher’s exact test. To analyse the group differences of the LEE scores between converters and non-converters, subjects with observation times shorter than 18 months and unknown outcomes (lost to follow-up) were assumed to be non-converters. Although this is a conservative assumption as conversion is the target outcome, the obtained results are, of course, of an explorative nature.

The associations of the LEE scores with the SIPS and COGDIS scores were calculated by the use of Spearman correlations. A two-sided α < 0.05 was considered significant. Multiple testing was adjusted by the Sidak correction. IBM SPSS-23 was used throughout the study; the C-index was calculated based on the special SPSS syntax [http://www-01.ibm.com/support/docview.wss?uid=swg21478383, assessed on 23 June 2017].

3. Results

3.1 Descriptive statistics of LEE

The shared variance of LEE subscales ranged from 9.6–46.7 percent (25.2–37.5 percent for ‘perceived irritability’) (Table S3). Only ‘perceived irritability’ differed significantly between the groups (Table 2). The mother was chosen as the most important person by a higher proportion of converters; this difference, however, was not statistically significant.

3.2 Correlation of LEE with psychopathology

The effect sizes of the associations between the LEE total, subscale scores, and baseline psychopathology were small; no correlation withstood the Sidak correction (Table S4).

3.3 Conversion rate

The mean observation period was 439.5 days (SD=162.2; median=548.0). At the 18-month follow-up, 36 of the 235 subjects had developed a psychotic disorder, resulting in an hazard rate (hr)= 0.188 (mean time to conversion=497.8 days, SE ±8.5, Cl95=481.1–514.4).

3.4 Predictive value of LEE variables

At univariate CRA, LEE ‘perceived irritability’ (p=0.011), ‘perceived lack of emotional support’ (p=0.026), and ‘total score’ (p=0.020) were shown to be significant predictors of conversion; ‘perceived criticism’, ‘perceived intrusiveness’, or ‘important person’ or ‘time of contact’, however, were not observed to be significant predictors (Table S5).

After entering all the LEE scales in stepwise multivariate CRA, only ‘perceived irritability’ (details of subscale in Table S6) remained in the model. The C-index was 0.62.

The explorative stratification of risk yielded two significantly different risk classes at a cut-off score > 10 (log-rank test ch²=5.728, p=0.017), with non-overlapping Cl95 bounds of time to conversion (risk class 1 [n=51; conversions=2]: hr=0.043,
mean=532.2 days, SE=11.2, CI95=510.3;554.1; risk class 2 [n=184, conversions=36]:
hr=0.223, mean=488.5 days, SE=10.3, CI95=468.4;508.6; Figure S2).

3.5 Revisiting the EPOS prediction model

The original EPOS prediction model (SIPS positive score>16, SIPS bizarre thinking score>2, SIPS sleep disturbance score>2, SIPS schizotypal personality disorder score, highest Global Assessment of Functioning (GAF-M) (Hall, 1995) score in the past year, years of education) appeared to be stable in the current dataset. Robustness of the model was successfully tested by the bootstrapping procedure. The C-index was 0.77.

Next, LEE perceived irritability was added to the original variables and remained in the model (stepwise forward/backward). No robust inter-correlation between the perceived irritability and the original variables emerged (Table S7). After bootstrapping, two variables of the original model were omitted as the β-Cl95 intervals crossed zero; these were 'highest GAF-M score in the past year' and 'SIPS schizotypal personality disorder score'. The final five-factor equation (Table 3) was used to calculate a PS for each subject as follows: (0.131 * [perceived irritability – 14.55]) + (1.193 * 'SIPS sleep disturbances >2') + (1.354 * 'SIPS bizarre thinking score > 2') + (1.756 * SIPS positive subscale score > 16) + (0.237 * [years of education – 12.49]). For consistency with the scaling of the other predictors, 'years of education' was inverted and, as LEE 'perceived irritability' was centered towards the mean. The C-index was 0.77 once again. Subsequently, the PS was stratified into three significantly different risk classes, with hazard rates ranging up to 0.91 (Table 4, Figure 1).

3.6 Effects of drug use and medication

Alike the original EPOS model (Ruhmann et al., 2010), the category 'Treated with AP only' (β=1.554, bias=0.100, SE=0.570, p<0.001, β-Cl95=−0.620;2.842, HR=4.732) was selected in the model while entering 'treatment' in Cox regression (stepwise forward); all five variables of the new model remained significant predictors. The category 'Any drug abuse' was not selected (stepwise forward).

4. Discussion

In investigating the perceived expressed emotion as a potential risk factor for developing the first psychotic episode, our study identified the LEE subdomain 'perceived irritability' as a significant predictor. This finding suggests that CHR individuals, who experience the most influential person in their social environment as more responsive to stress and less able to cope with it are more likely to convert to psychosis. The impact of socio-environmental dynamics reflected by 'perceived irritability' was further demonstrated by more than a 500-percent increase of the hazard rate for the risk class 1 to the risk class 2, therefore, pointing towards a dose-related effect. Furthermore, perceived irritability shared only marginal variance with the other LEE domains and thus proved rather independent.

The predictive value of 'perceived irritability' was further underpinned by its robust selection into the original EPOS model (Ruhmann et al., 2010). The respective C-index of 0.77 for the modified EPOS model was comparable to the C-index of 0.71 for a model reported recently by the North American Prodrome Longitudinal Study (NAPLS-2) (Cannon et al., 2016) and the values reported for the prediction models currently used in somatic medicine (Kattan et al., 2013; Ross et al., 2002). The original EPOS
model yielded an equivalent C-index; yet, the new model achieved better risk enrichment in the highest class (hr=0.91 versus 0.85) and a significant difference between all the risk classes. The fact that 'perceived irritability' replaced two variables of the original EPOS model ('SIPS schizotypal personality disorder' and 'highest GAF-M score in past year') is noteworthy considering the support of these two variables in other studies (discussed in detail in the work of Ruhrmann et al., 2010)). Functional deficits, in particular, have been reported as parts of prediction models (Fusar-Poli et al., 2015). Replacement of such variables once again underlines the relevance of socio-environmental disturbances assessed by this psychological construct—at least with regard to an imminent 18-month risk. A reason might be that 'perceived irritability' can be considered a risk factor, which is even active during the risk period, whereas the other two variables could primarily be viewed as risk indicators. The new prediction model was robust in the presence of potentially confounding antidepressants or antipsychotics prescribed to 41 percent of the sample. Since EPOS was a naturalistic study, psychopharmacological treatment was only retrospectively recorded in a 9- to 18-month follow-up; detailed information was thus not always available; this has to be considered a limitation. Alike NAPLS (Cannon et al., 2008) and supported by earlier analyses in the EPOS sample (Ruhrmann et al., 2010), the statistical result for antipsychotics probably reflects the decision of clinicians to prescribe antipsychotics to patients presented with more severe psychosis-like symptoms on the verge of conversion. Abnormal stress-reactivity has been demonstrated in relatives of psychosis patients and familial stress-reactivity was suggested as a vulnerability marker for psychotic illness (Aiello et al., 2012; Lataster et al., 2010; Myin-Germeys et al., 2001). Hence, the results should be transferable to CHR families. Increased stress-reactivity of siblings even correlated with positive symptoms in psychosis patients (Lataster et al., 2010). This result seems to correspond to the association that we observed between higher levels of perceived susceptibility to stress in influential subjects with a higher risk for conversion during follow-up. Unexpectedly, neither criticism nor over-involvement, which are usually associated with unfavourable effects on the course of manifest psychosis, the nature of "influential person", or the time spent with them were shown to be important. This seems to be in line with the hypothesis of Tarrier et al., 1988, who had already postulated that being opposed to family pathology or dysfunction, the influence of EE was primarily a result of the level of stress of EE produced on the immediate environment. Observing dysfunctional stress coping of others might even lead to a dysfunctional model learning and consequently impede the coping of CHR patients in a period characterized by threatening experiences (Rapado-Castro et al., 2015). Such a socio-environmental condition may further increase the level of uncertainty, which is described as a core feature of the prodromal phase (Conrad, 2015; Kapur, 2003; Klosterkötter, 1988) and, therefore, contribute to the heightened stress level observed in CHR patients (Pruessner et al., 2011; Walker et al., 2013)—an effect that may even be intensified by the increased stress reactivity observed in this group (Phillips et al., 2012). The assumed association between 'perceived irritability', the stress response of CHR patients, and the increased risk for a conversion to psychosis is in line with the diathesis-stress model (Walker and Diforio, 1997) and is further supported by studies showing a correlation between the level of EE and the neurophysiological stress response in schizophrenia (Altorker et al., 1998; Sturgeon et al., 1981; Tarrier and Barrowclough, 1984; Tarrier et al., 1988; Tarrier et al., 1979). To further explain this association, a more sensitive monitoring of the interaction of EE, subjective stress and
psychopathology would be required, e.g., the longitudinal Experience Sampling Method (Myin-Germeys et al., 2009). The (subjective) impression that support cannot be sufficiently provided by “irritable” persons may lead to a reactive reduction of support-seeking behaviour, as was observed in a study on depressed patients showing a negative correlation between LEE 'perceived irritability' and support-seeking behaviour, with a large effect size (Gerlsma and Hale, 1997). Reduced help-seeking, in turn, might contribute to well-known social withdrawal behaviour in CHR patients (who, in addition, are often depressed) (Fusar-Poli et al., 2013), which further increases the risk of conversion to psychosis (Nieman et al., 2013; Velthorst et al., 2010). Furthermore, resilience may be considerably diminished, given the significance of social support as a protective factor in mental health (Berkman and Syme, 1979; DeLongis et al., 2004).

Two studies on FEP reported a positive correlation between the duration of untreated illness or the duration of untreated psychosis, and the level of criticism in relatives. Remarkably, in the second study, only 23 percent of the relatives scored high on criticism. Furthermore, a cross-sectional study observed a marked increase of critical comments in the relatives of patients suffering from the illness for 3–5 years in comparison to relatives of treated FEP patients (Hooley, 2007). A state-dependence of the level of criticism is also suggested by a decline of EE levels after the index patients are discharged from the hospital. Consequently, perceived criticism should also be state-dependent, which could explain the finding in our CHR sample. The lacking effect of over-involvement is in line with the inconsistent findings of the impact of this specific EE aspect on the clinical status of patients (Koutra et al., 2015).

In close relationships, the perception of others can be biased. In our study, a bias may have been induced by lower stress tolerance as discussed above. The broad range of assessments already implemented in EPOS limited the further investigation of this aspect. To disentangle the objective socio-environmental share of perceived irritability from the subjective share, future studies should combine subjective appraisal with the independent observations of the relatives’ behaviour, consisting of their interaction with the patient and their observable coping with challenging situations. This would not only require additional information, as provided by the CFI (Hooley and Parker, 2006), but also controlled social-psychological experiments. Such a design could also evaluate the differences between the observation-based and patient-based appraisal of criticism and over-involvement. However, as the subjective appraisal of and coping with social interactions should be decisive for the level of individual stress, the perceived EE could be the superior indicator for the impact of such interactions on the risk for psychosis.

The generally lacking effect of the type of important person in our study is in line with most EE studies that do not report a specific effect of the type of reference person (e.g., Cole and Kazarian, 1993)). A different finding was reported by King and Dixon, 1999 who found that the relapse rate in young schizophrenia patients was best predicted by criticism expressed by the father and over-involvement expressed by the mother. In our study, although the proportion of CHR subjects reporting their mothers as most important person was numerically (though not statistically) higher in the converter group, no predictive effect of ‘over-involvement’ emerged.

Culture seems to affect prevalence rates and the pattern of EE as well as to moderate clinical outcomes associated with EE as reported in a review by Hooley, 2007. Even in CHR individuals, EE effects moderating the impact of culture were reported (Tsai et al., 2015). Therefore, we statistically controlled all our analyses for this and other site
effects. However, the transcultural generalizability of our results, especially with regard to non-European cultures, requires further research.

One item was erroneously omitted from the German LEE version. As demonstrated in the Method section, it can be assumed that this error was successfully compensated by imputation and thus had no significant effect on our results.

Splitting our sample for cross-validation was not an option with regard to the statistically required number of conversions to psychosis, bringing up overfitting as a potential issue. However, the results of the extensive bootstrapping procedure already indicated a good internal validity of the model and the number of seven events per variable was sufficient (Vittinghoff and McCulloch, 2007).

Conclusion
In summary, the ‘perceived irritability’ of a key relative, as assessed by the LEE, was found to be a predictor of conversion for high-risk patients into first-episode psychosis. As a part of the revised EPOS model, risk prediction was considerably improved by defining a high-risk class with a hazard rate above 0.90. Considering EE as both risk indicator and factor could, therefore, contribute to individualized prediction and help enhance the success of preventive psychological interventions (Schmidt et al., 2015; van der Gaag et al., 2012) by offering stress management not only for the patient but also for their family members.

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SR, JK, FSL, MB, RKRS and DL designed the study; TH, MR and SR managed the literature searches, undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript. All other authors declare that they have no conflicts of interest.
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**Figures legends**

**Figure 1**: Survival times of the risk classes built on the LEE irritability score alone (Kaplan–Meier Analysis); blue colour: score ≤ 10 (hr = 0.043); red colour: score > 10 (hr = 0.223).

**Table 1**: Demographic and clinical characteristics

**Table 2**: Psychometric data of LEE total and subscale scores by comparing converters and non-converters

**Table 3**: Cox proportional hazards model (based on the predictors included in the earlier EPOS prediction model and the LEE irritability score)

**Table 4**: Revised Prognostic Index for risk stratification