Emerging symptoms on the pathway to psychosis

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Depressive symptoms are associated with (sub) clinical psychotic symptoms in patients with non-affective psychotic disorder, siblings and healthy controls.

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Depressive symptoms are associated with (sub) clinical psychotic symptoms in patients with non-affective psychotic disorder, siblings and healthy controls.

**Verbal impression chapter 5 from a young blogger**

“Waarom vinden we het zo normaal dat we op onze ouders kunnen lijken, maar duurt het even voordat we snappen dat dat bij psychoses ook weleens zo zou kunnen werken? Want als mijn broer en ik op elkaar lijken omdat we dezelfde ouders hebben, zijn er dan ook overeenkomsten tussen ons tweeën in die dingen die bij een psychose meespelen? Blijkbaar wel. Depressieve symptomen, die vaak gepaard gaan met psychoses, zijn meer aanwezig in broers of zussen van mensen die een psychose hebben (gehad) dan bij mensen die geen bloedverwant zijn van mensen met een psychotisch verleden. Lijken we dus nog meer op elkaar dan we dachten.”

“Why are we so used to the idea that we resemble how our parents look, but does it take longer to realize that psychoses could work that way just as well? Because if my brother and I have similar features in our appearance because we have the same parents, does that mean we have those things in common that come into play with a psychosis? Apparently so. Symptoms of depression, often coupled with psychoses, are represented higher among siblings with those who have (had) a psychosis, than with those that have no relatives with psychotic symptoms. Evidently we’re more alike than we would’ve thought.”

Bas Boshuizen
Blogger www.nietgek.nl
Zie ook: www.visitingmissouri.net
Abstract

**Background:** Depression is a clinically relevant dimension, associated with both positive and negative symptoms, in patients with schizophrenia. However, in siblings it is unknown whether depression is associated with subclinical positive and negative symptoms.

**Method:** Depressive symptoms and their association with negative and positive symptoms were examined in 813 healthy siblings of patients with a non-affective psychotic disorder, 822 patients and 527 healthy controls. Depressive episodes meeting DSM-IV-TR criteria (lifetime), and depressed mood (lifetime) were assessed with the Comprehensive Assessment of Symptoms and History (CASH) in all three groups. In the patient group severity of positive and negative psychosis symptoms was assessed with the CASH. In the siblings, and healthy controls, severity of sub-clinical psychosis symptoms was assessed with the Community Assessment Psychic Experiences (CAPE).

**Results:** Patients reported more lifetime depressed mood and more depressive episodes than both siblings and controls. Siblings had a higher chance of meeting lifetime depressive episodes than the controls; no significant differences in depressed mood were found between siblings and controls. In all three groups the number and duration of depressive symptoms were associated with (sub) clinical negative symptoms. In the patients and siblings the number of depressive symptoms was furthermore associated with (sub) clinical positive symptoms. Finally, lifetime depressed mood showed familial clustering, but this clustering was absent for lifetime depressive episodes.

**Conclusions:** These findings suggest that a co-occurring genetic vulnerability for both depressive and psychotic symptomatology, on a clinical as well as subclinical level exists.
Chapter 5

Introduction

Depression and positive symptom dimensions in psychosis are considered to be separate though interrelated dimensions of psychotic disorder (Krabbendam et al. 2004; van Os & Kapur, 2009) and are closely related on all levels of the psychosis continuum (Wigman et al. 2011). Clinically, this is reflected by diagnoses such as schizoaffective or mood disorders with psychotic features, in which depressive and psychotic symptoms co-occur. Depression is a commonly reported symptom in the prodromal phase of psychotic illness, (Häfner et al. 2005; Iyer et al. 2008) and has been shown to be associated with a transition to psychosis in ultra-high risk samples (Yung et al. 1998, 2003, 2004). In addition, in general population samples, subclinical psychotic symptoms and depression are associated in both adolescents (Yung et al. 2006; Armando et al. 2010; Mackie et al. 2011; Wigman et al. 2011) and adults samples (Krabbendam et al. 2004). Furthermore, the presence of depressive symptoms in combination with hallucinatory experiences in the general population increases the risk for a later diagnosis of clinical psychosis (Krabbendam et al. 2005).

Depression is a clinically relevant dimension in patients with schizophrenia with a prevalence range of 6% to 75% (average of 25%) during the course of the illness (Sands & Harrow, 1999; Peralta & Cuesta, 2001; Siris & Bench, 2003; Häfner et al. 2005; van Os, 2009). In the fully developed schizophrenia syndrome, depression has been associated with outcome (Häfner et al. 1999, Sands & Harrow, 1999; Conley et al. 2007), higher relapse rates (Birchwood et al. 1993), and increased risk of suicide (Siris, 2001; Lindenmayer & Khan, 2006).

A greater insight into the relationship between psychosis and depression can be obtained by measuring depressive symptoms and their associations with (subclinical) psychotic symptoms in siblings at genetic risk of psychosis. Siblings of patients with schizophrenia are at increased risk for psychosis, yet do not suffer from the consequences of having a chronic and disabling disorder or treatment. In addition, In addition, a higher prevalence of subclinical expression of psychotic vulnerability is found in siblings (Kendler et al. 1995; Fanous et al. 2001; Arajärvi et al. 2006; Smith et al. 2008). However, data on the prevalence of depression amongst siblings (including twins) are scarce. The majority of studies reported to date have used small numbers and their results are contradictory. Lee et al. (2008) reported that relatives of patients with schizophrenia experienced more difficulties recovering from unpleasant moods compared to healthy controls. Chang et al. (2002) and Mortensen et al. (2010) both
found a higher risk for depression amongst siblings. Argypoulos and colleagues (2008) found that co-twins of schizophrenia probands are more likely to be diagnosed with anxiety and depression disorders, compared to control twins. However, other studies have not demonstrated a higher depression rate amongst siblings (Arajärvi et al. 2006) and twins of schizophrenia patients (Lyons et al. 2000) compared to healthy controls. We are not aware of investigations of the associations between depressive symptomatology and (sub) clinical psychotic symptoms in siblings of patients with non-affective psychotic disorders.

In the present study we report on the presence of, and relationship between, depressive symptoms and (sub) clinical positive and negative symptoms in a large cohort of non-psychotic siblings, their psychotic probands and healthy controls. The data was obtained in the Genetic Risk and Outcome in Psychosis (GROUP) project. Our study focussed on three questions:

1) Is lifetime presence of depressed mood or lifetime depressive episodes according to DSM-IV more prevalent in patients with a non-affective psychotic disorder, as well as in their siblings, in comparison with healthy controls?

2) Are the severity and duration of depressive episodes associated with (sub) clinical levels of positive and negative symptoms in all three groups?

3) Is there a familial clustering of lifetime presence of depressed mood or lifetime depressive episodes according to DSM-IV?

**Methods**

**Participants**

The study sample consisted of patients with a diagnosis of non-affective psychotic disorder, their siblings, and controls from the general population in the context of the Dutch national GROUP project (Korver et al. 2012). Patients from selected geographical areas in the Netherlands and Belgium were identified through a number of representative clinicians whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services either as out-patients or in-patients were recruited for the study. First-degree relatives were sampled through participating patients. Control subjects were recruited through random mailings as
well as advertisements in local newspapers. Written informed consent conforming to the guidelines approved by the local ethics committee was obtained from all subjects. We note that no participants from the Groningen site were included here because the Groningen site used the Schedules for Clinical Assessment for neuropsychiatry (SCAN) instead of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992) (Korver et al. 2012)

The inclusion criteria for the GROUP study were: fluency in Dutch; age in the range 16 to 55 years and additionally for the patients, a DSM-IV diagnosis of non-affective psychotic disorder, assessed by clinical interview with the CASH, and first contact with mental health facilities within the last ten years. At least one sibling of each patient was required to take part in the study. The sibling non-patient status was defined as the absence of any lifetime psychotic disorder by CASH interview. Participants in the control group lacked a personal psychotic disorder (CASH interview) and in addition did not have a first-degree family member with the Family Interview for Genetic Studies (FIGS) with themselves as informant (NIMH, 1992). It should be noted that some controls were related. This was controlled for by using multilevel analyses.

**Measures**

The sections on affective and psychotic disorders of CASH (Andreasen et al. 1992) were used to confirm a) the presence of a diagnosis of non-affective psychosis in patients; b) the absence of such a diagnosis in their relatives; and c) the absence of a lifetime diagnosis of any psychotic disorder or any current affective disorder in the healthy controls. Furthermore, presence of lifetime depressed mood for a minimum of two consecutive weeks, as well as lifetime presence of clinical depression according to DSM-IV-TR criteria, were derived from the CASH interview. Both depression measures (depressed mood and depressive episodes) were dichotomous (0 = absent/ not meeting criteria, 1 = present/ meeting criteria). The severity of depression was characterized by the duration of the longest depressive episode lifetime and number of depressive symptoms during the longest lifetime depressive episode. Both the duration and the number of symptoms were considered as continuous variables, where the duration ranged from 0 to 997 days and the number of symptoms ranged from 0 to 8. In addition, positive and negative psychotic symptoms in the patient group were derived from CASH. The weighted mean of a global evaluation of severity of lifetime delusions and lifetime hallucinations constituted the Positive Clinical Symptom Scale; a continuous variable
ranging from 0 to 5 (0 = none, 1 = doubtful, 2 = mild, 3 = moderate, 4 = considerable, and 5 = severe). The weighted mean of a global evaluation of severity of lifetime apathy and asociality constituted the Negative Clinical Symptom Scale; a continuous variable ranging from 0 to 5 (0 = none, 1 = doubtful, 2 = mild, 3 = moderate, 4 = considerable, and 5 = severe).

The Community Assessment of Psychic Experiences (CAPE) (Stefanis et al. 2002; Konings et al. 2006) is a 42-item self-report measurement of psychotic experiences in the general population. CAPE assesses the frequency on a scale of 0-3 (from ‘never’ to ‘almost always’) of lifetime subclinical psychotic experiences, as well as the distress associated with these symptoms also on a 0-3 scale (from ‘no distress’ to ‘much distress’). The weighted mean of the positive subclinical symptom frequency items constituted the Positive Subclinical Symptom Scale and the weighted mean of the negative subclinical symptom frequency items constituted the Negative Subclinical Symptom scale for the sibling and control groups.

Statistical Analysis

First, we investigated the association between group (controls, siblings and patients) and depression. Multilevel logistic regression models were employed with the categorical variable group (0 = controls, 1 = siblings, 2 = patients) as the independent variable and the two dichotomous measures of depression (depressed mood and depressive episodes) as dependent variables. Multilevel analyses were used because the patients and siblings, and also some of the controls, were related, thus invalidating the assumption of independence of observations and requiring conservative adjustment of standard errors for hierarchical clustering within families. Data were analyzed using the XTGEE routine in STATA 11.0 (StataCorp, 2009). All analyses were corrected a priori for a possible confounding effect of age and sex.

In a second analysis, the association between depression and (sub) clinical psychotic symptoms in the three groups was tested separately using multilevel regression models (using XTREG routine in STATA 11.0). The two depression severity variables were the dependent variables in all three groups. The independent variables in the patient group were the two clinical psychosis symptom dimensions (positive and negative symptoms) of the CASH, while for the sibling and control groups the two subclinical symptom dimensions of the CAPE (positive and negative symptoms) were used. All independent variables were first put in the regression model(s) separately and at a second stage
jointly, in order to assess the independence of associations. All analyses were corrected \textit{a priori} for age and sex.

Lastly, the familial clustering of depression was assessed using logistic regression models with the two CASH depression variables (depressed mood and depressive episodes) in the patient serving as independent variables, and with the same two CASH depression variables in their sibling(s) as dependent variables.

We thus performed a total of nine tests; as we tested research questions based on a-priori assumptions, we chose not to correct for multiple comparisons. The level of significance is therefore $p=0.05$. However, in order to allow for a conservative interpretation of the presented data, we point out that the Bonferroni ($N=9$) corrected level of significance would be $0.006$.

\section*{Results}

\subsection*{Sample characteristics}

The first and the third analyses above were performed on a total of 822 patients, 813 of their siblings and 527 control participants. However, as data was on the variables used in the second analyses was not available for all participants, only 607 patients, 684 siblings, and 493 control participants were included in the second analyses. The socio-demographic and clinical characteristics of the three groups are described in table 1. The depression variables are displayed in table 2 and the psychosis (sub) clinical symptoms variables in table 3.

\subsection*{The association between psychosis vulnerability and depression}

Multilevel logistic regression analyses showed an association between group and depressed mood ($\chi^2 = 344.4, p < 0.0001$). The patients reported more depressed mood compared to the controls (OR $= 7.8$, 95\% confidence interval (CI) $5.96 - 10.14$, $p < 0.0001$) and the siblings ($\chi^2 = 275.8$, $p < 0.0001$). No significant difference in depressed mood was found between siblings and controls (OR $1.22$, 95\% CI $0.95 - 1.57$, $p < 0.116$). Both the patients and the siblings had a significantly increased risk of depressive episodes compared to the control participants (patients compared to controls: OR $8.9$, 95\% CI $6.81 - 11.67$, $p < 0.0001$; siblings had borderline significantly increased risk compared to
controls: OR 1.28, 95% CI = 1.00 – 1.65, p = 0.050). Furthermore, the patients exhibited a significantly increased risk of depressive episodes as compared to the siblings ($\chi^2 = 363.3$, p < 0.0001).

**Depression severity and its association with (sub) clinical psychosis symptom dimensions**

Multilevel regression analyses showed that the duration of the longest depressive episode in the patient group was associated significantly with positive clinical psychosis symptoms ($\beta = 11.22, 95\%\ CI\ 1.49 \text{ – } 20.94, p < 0.024$) and negative clinical psychosis symptoms ($\beta = 16.08, 95\%\ CI\ 7.48 \text{ – } 24.67, p < 0.0001$). However, on introducing both independent variables into a single regression model, it was found that negative clinical

### Table 1 Sociodemographic and clinical sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 822)</th>
<th>Siblings (n = 813)</th>
<th>Controls (n = 527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>28 (8.1)</td>
<td>28 (8.6)</td>
<td>29 (10.6)</td>
</tr>
<tr>
<td>Range</td>
<td>15-61</td>
<td>14-60</td>
<td>15-56</td>
</tr>
<tr>
<td>Proportion of men (%)</td>
<td>77</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Primary DSM-IV diagnosis (lifetime), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>555 (68)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>108 (13)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>29(4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>82 (10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other non-affective psychotic disorders</td>
<td>48(5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mood disorders (in full remission), n (%)</td>
<td>-</td>
<td>129 (16)</td>
<td>55 (10)</td>
</tr>
<tr>
<td>Meeting DSM criteria for current depressive episode, n (%)</td>
<td>92 (12.4)</td>
<td>13 (1.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>No psychopathology, n (%)</td>
<td>-</td>
<td>684 (84)</td>
<td>472 (90)</td>
</tr>
<tr>
<td>Antipsychotics, n (%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Not currently using</td>
<td>99 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently using</td>
<td>643 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>14(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Not currently using</td>
<td>609 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently using</td>
<td>213 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood stabilizers, n (%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Not currently using</td>
<td>782 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently using</td>
<td>40(5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S.D., Standard deviation; NOS, not otherwise specified.
Table 2: Scores on CASH depression variables

<table>
<thead>
<tr>
<th></th>
<th>Patients Total</th>
<th>Male</th>
<th>Female</th>
<th>Relatives Total</th>
<th>Male</th>
<th>Female</th>
<th>Controls Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis 1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>822</td>
<td>631</td>
<td>191</td>
<td>813</td>
<td>365</td>
<td>448</td>
<td>527</td>
<td>237</td>
<td>290</td>
</tr>
<tr>
<td>Presence of lifetime depressive mood, n (%)</td>
<td>584 (71)</td>
<td>434 (65)</td>
<td>150 (76)</td>
<td>259 (32)</td>
<td>95 (28)</td>
<td>164 (40)</td>
<td>149 (29)</td>
<td>49 (21)</td>
<td>100 (34)</td>
</tr>
<tr>
<td>Presence of lifetime clinical depression according to DSM-IV-TR criteria, n (%)</td>
<td>603 (73)</td>
<td>446 (71)</td>
<td>157 (82)</td>
<td>269 (33)</td>
<td>101 (28)</td>
<td>168 (38)</td>
<td>152 (29)</td>
<td>45 (19)</td>
<td>107 (37)</td>
</tr>
<tr>
<td>Analysis 2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>607</td>
<td>455</td>
<td>152</td>
<td>684</td>
<td>309</td>
<td>375</td>
<td>493</td>
<td>223</td>
<td>270</td>
</tr>
<tr>
<td>Duration of the longest depressive episode lifetime (years), mean (s.d.)</td>
<td>1129 (160.0)</td>
<td>104.8</td>
<td>137.3</td>
<td>41.4 (112.5)</td>
<td>26.9 (85.9)</td>
<td>54.4</td>
<td>36.4 (113.7)</td>
<td>24.6 (102.3)</td>
<td>44.4</td>
</tr>
<tr>
<td>Number of depression symptoms during the longest lifetime depressive episode, mean (s.d.)</td>
<td>5.1 (2.4)</td>
<td>4.9 (2.4)</td>
<td>5.7 (2.1)</td>
<td>1.8 (2.6)</td>
<td>1.4 (2.3)</td>
<td>2.2 (2.8)</td>
<td>1.5 (2.3)</td>
<td>0.93 (1.8)</td>
<td>2.0 (2.6)</td>
</tr>
</tbody>
</table>

CASH, Comprehensive Assessment of Symptoms and History; s.d., standard deviation. a Range 0-998. b Range 0-8.

Table 3: Scores on CASH (patients) and CAPE (siblings and controls) (subclinical psychosis symptom variables)

<table>
<thead>
<tr>
<th></th>
<th>Patients Total</th>
<th>Male (n = 607)</th>
<th>Female (n = 152)</th>
<th>Relatives Total</th>
<th>Male (n = 684)</th>
<th>Female (n = 375)</th>
<th>Controls Total</th>
<th>Male (n = 493)</th>
<th>Female (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive clinical psychosis symptoms (range 0-5)</td>
<td>3.3 (1.31)</td>
<td>3.2 (1.33)</td>
<td>3.5 (1.25)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative clinical psychosis symptoms (range 0-5)</td>
<td>2.3 (1.46)</td>
<td>2.3 (1.45)</td>
<td>2.4 (1.51)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Positive subclinical psychosis symptoms (range 0-3)</td>
<td>0.02 (0.20)</td>
<td>0.19 (0.18)</td>
<td>0.21 (0.21)</td>
<td>0.18 (0.18)</td>
<td>0.16 (0.18)</td>
<td>0.18 (0.19)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative subclinical psychosis symptoms (range 0-3)</td>
<td>0.54 (0.37)</td>
<td>0.53 (0.34)</td>
<td>0.55 (0.40)</td>
<td>0.46 (0.31)</td>
<td>0.44 (0.29)</td>
<td>0.48 (0.32)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CASH, Comprehensive Assessment of Symptoms and History; CAPE, Community Assessment Psychic Experiences. Values given as mean (standard deviation).
psychosis symptoms remained associated with the duration of the longest depressive episode ($\beta = 14.35$, 95% CI 5.27 – 23.43, $p < 0.002$), whereas positive clinical psychosis symptoms were not ($\beta = 6.00$, 95% CI -4.22 to 16.22, $p < 0.250$). Slightly different results were obtained when considering the number of depressive symptoms during the longest depressive episode. Both positive ($\beta = 0.47$, 95% CI 0.33 – 0.61, $p < 0.0001$) and negative clinical psychosis symptoms ($\beta = 0.55$, 95% CI 0.43 – 0.67, $p < 0.0001$) were significantly associated with the number of symptoms in the patient group. The same conclusion was reached when both independent variables were entered into a single model.

The results for the sibling group were similar to those of the patients. The duration of the longest depressive episode was significantly associated with both positive ($\beta = 87.32$, 95% CI 45.71 – 128.93, $p < 0.0001$) and negative subclinical symptoms ($\beta = 67.09$, 95% CI 45.21 – 88.96, $p < 0.0001$). When both independent variables were entered into a single model, only the negative subclinical symptoms retained a significant association (negative symptoms: $\beta = 58.94$, 95% CI 33.21 – 84.66, $p < 0.0001$; positive symptoms: $\beta = 28.98$, 95% CI -19.29 – 77.25, $p < 0.239$). The number of depressive symptoms was significant in the model of positive ($\beta = 3.73$, 95% CI 2.79 – 4.67, $p < 0.0001$) and negative subclinical symptoms ($\beta = 2.84$, 95% CI 2.37 – 3.31, $p < 0.0001$) and both symptoms remained significant when entered together in one model.

The results for the control group differed from those of the siblings and the patients. In the control group, the duration of the longest depressive episode was significant in the model of negative subclinical symptoms ($\beta = 47.13$, 95% CI 15.00 – 79.25, $p < 0.004$) but not in the model of positive subclinical symptoms ($\beta = -0.30$, 95% CI -58.55 – 57.94, $p < 0.992$). The number of depressive symptoms was significant in the model of positive ($\beta = 2.17$, 95% CI 1.04 – 3.30, $p < 0.0001$) and negative subclinical symptoms ($\beta = 2.08$, 95% CI 1.47 – 2.68, $p < 0.0001$). When both are entered into a single model, only the negative symptoms remained significant (negative: $\beta = 1.89$, 95% CI 1.22 – 2.55 $p < 0.0001$; positive: $\beta = 0.82$, 95% CI -0.36 – 2.01, $p < 0.174$).

In this way we identified an association between depression and negative (sub) clinical symptoms in all three groups. In addition we found an association between number of depressive symptoms and positive (sub) clinical psychotic symptoms but only in the patients and the siblings.
Multilevel logistic regression analysis showed that depressed mood in patients was significantly associated with depressed mood in their sibling(s) (OR 1.54, 95% CI 1.14 – 2.08, p < 0.005). Depressive episodes did not show familial clustering (OR 1.22, 95% CI 0.92 – 1.62, p < 0.177).

**Discussion**

In this study we investigated the presence of, and relationship between, depressive symptoms and (sub) clinical psychotic symptoms in a cohort of patients with a psychotic disorder, their siblings, and healthy controls. We found that patients reported more depressed mood compared to controls and siblings, whereas the siblings did not differ from the controls. Both patients and siblings exhibited a significantly increased risk of depressive episodes compared to the controls. The *duration* of the longest depressive episode was found to be associated with negative but not positive clinical psychosis symptoms in patients. However, the *number* of depressive symptoms was associated with both positive and negative clinical psychosis symptoms. Similar results were found for the siblings whereas in the controls only negative subclinical psychosis was associated with the duration of the depressive episode and the number of depressive symptoms. Finally, we found evidence for familial clustering at the level of depressed mood, but not for depressive episodes.

The findings of a higher rate of depression in siblings compared to the controls are in line with Argyropoulos *et al.* (2008). Nonetheless, they are at odds with a study of siblings showing similar rates of depression in siblings compared to controls (Arajärvi *et al.* 2006). The higher average age of the participants in the latter study may explain the discrepancy as the majority of the non-psychotic siblings had already exceeded the age-related risk window for developing a psychosis. We are not aware of earlier studies of the association between depression and negative and positive psychotic symptoms in siblings. Our findings are in line with other results in populations with psychotic disorder (Norman & Malla, 1991; Messias *et al.* 2001; Freeman & Garety, 2003; Drake *et al.* 2004). However, as far as the healthy controls are concerned, our results show a partial correspondence with other studies. Earlier studies in the general population revealed an association between depressive, negative and positive symptoms (Stefanis
et al. 2002; Krabbendam et al. 2004, 2005), contrasting with our finding of an association with negative symptomatology only. We note that while a weighted mean of all subclinical symptoms present in the CAPE was used in the study reported here, the former studies utilized a different methodology: only one positive symptom would identify positive psychotic symptoms.

The results in our study suggest that the duration of depression is only associated with the negative psychosis domain in patients and siblings, whereas the number of depressive symptoms is associated with negative as well as positive psychosis symptoms. These observations are difficult to explain in a straightforward way. They may be understood in the light of the different temporal dynamics of positive and negative psychosis. Clinically, positive symptoms tend to wax and wane over time, as well as depressive symptoms, whilst negative symptoms present themselves more continuously, in a trait-like fashion. Since negative symptoms and depressive symptoms also show overlap (Siris, 2000), negative symptoms may found to be associated with the duration of depression. However, the co-occurrence of these symptom dimensions may also be explained by the phenomenon that raters are liable to rate conceptually similar phenomena (i.e. ‘blunted affect’ as observed in negative symptoms versus ‘depressed mood’ as seen in depression) in an equal way. This obviously also relates to the important issue whether depressive phenomena and (negative) psychotic phenomena are truly separate concepts.

The results of our study suggest that depressive symptoms are not simply a manifestation of the co-morbidity of schizophrenia or part of the risk phase of a psychosis, but are inherently related to especially negative (sub) clinical symptoms. This is in line with the suggestion that psychosis consists of multiple domains (positive, negative, cognitive and affective symptoms (Van Os and Kapur; 2009). These domains fit in a continuous (subclinical) model in which correlated psychopathology dimensions (as seen in patients) are also apparent in risk groups and general population groups, only to a lesser extent. (van Os et al. 2000, 2009). Our findings underscore the presence of an interrelated depressive mood – (sub) clinical negative psychosis continuum. It has been suggested that subclinical psychotic experiences and depression are interwoven phenomena that co-occur (Wigman et al. 2011). This previous finding is in line with suggestions that levels of depression mirror levels of subclinical psychotic experiences in the general population (Yung et al. 2009; Wigman et al. 2011). Our present study supports these findings, but extends them by demonstrating that depressive phenomena
are specifically related to the negative symptom domain. The overlap between negative and depressive symptomatology might play a role in this. This study has shown an existing shared vulnerability in families with schizophrenia for both depressed mood (one of the major symptoms in a depression) and positive and negative (sub) clinical symptoms. It might point at a familial vulnerability in families with schizophrenia for both depression and psychosis. The found associations between negative, positive and depressive symptoms in siblings (on a subclinical level) as well as in patients (on a clinical level) also point at an overlap between the two concepts: depression and psychosis: there seems to be a shared risk which also is expressed at a subclinical level. In siblings subclinical psychotic experiences and depressive symptoms may be an expression of interrelated aspects of the same underlying factor also seen in patients.

From a clinical point of view our findings are relevant: firstly to underscore the increased risk of a depressed mood and a depressive episode for patients suffering from a psychosis. Determining the temporal appearance, duration and severity of depressive symptoms is necessary for diagnosis and planning treatment. A study by Yung et al. (2007) showed an association between a reduction of depressive symptoms and a reduction of psychotic like experiences. Treating depression may include pharmacological and psychosocial intervention. Because depressive symptoms may herald psychotic relapse, patients with depressive symptoms should be monitored carefully. Second, our results suggest that some of the healthy siblings (those with more depressive symptoms) are more at risk for psychosis then other siblings: they have three risk factors: age, genetic liability and depressive symptoms (Hansen et al. 2005; Johnstone et al. 2005, Owens et al. 2005, Yung et al. 2007).

Our results should be interpreted in the light of the following limitations: Our data are cross sectional and as such do not provide evidence regarding of the causal role of depressive symptoms on psychosis or vice versa. Another potential limitation is the difficulty in differentiating between negative and depressive symptoms, causing a risk for overlap. In addition, because of the age of our group, some of the unaffected siblings are at risk of developing psychosis.

We also need to consider several potential limitations of the GROUP study in general. The first is a selection bias: participants willing to participate in a demanding study protocol may be different from participants in other less demanding studies, or from subjects refusing participation in research. Controls and siblings could have a current depressive episode; however, having a current depressive episode may have reduced
the chance of participation in a study. Another selection bias is the exclusion of patients without brothers or sisters.

Second, differences between relatives and healthy controls may be difficult to detect because not all siblings of a specific patient are included, and siblings with more subclinical symptoms may have been more reluctant to participate in the GROUP study.

Third, inter-rater reliability remains a vulnerability in large multisite studies. Within the GROUP project the interrater reliability of the most important diagnostic instruments was assessed. Interrater reliability of the diagnostic classification according to DSM-IV as measured by the CASH was satisfactorily, based on assessing the concordance between the CASH diagnosis and the diagnosis as assessed by the treating clinician. A randomly selected comparison of 65 subjects with a psychotic disorder revealed a difference in diagnosis in only one case. However, the specific interrater reliability of negative and depressive symptoms was not assessed, and this is a limitation. Interrater reliability of the CAPE is not an issue, as this is a self-report questionnaire.

Fourth, in this study we did not have the data on relevant medication for the siblings and controls. As these may influence the severity and the course of the symptoms this should be regarded as a limitation.

In conclusion we have shown siblings and patients to be more at risk of a depressive episode and their depressive symptoms are associated with positive and negative (sub) clinical psychotic symptoms. These findings suggest that a co-occurring genetic vulnerability for both depressive and positive and negative psychotic symptomatology, on a clinical as well as subclinical level exists. Clinically the question of the efficacy of treatment of depressive symptoms in siblings for reducing (sub) clinical psychotic symptoms and risk of transition to overt psychosis merits further studies. Finally, to investigate the relationship between depressive and subclinical psychotic symptoms in siblings over time, longitudinal data are required.

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Depressive symptoms are associated with (sub) clinical psychotic symptoms


