Schizophrenia Bulletin vol. 38 no. 2 pp. 247–257, 2012
doi:10.1093/schbul/sbr196
Advance Access publication on January 18, 2012

Evidence That Psychotic Symptoms Are Prevalent in Disorders of Anxiety and Depression, Impacting on Illness Onset, Risk, and Severity—Implications for Diagnosis and Ultra–High Risk Research

Johanna T. W. Wigman[1,2], Martine van Nierop[2], Wilma A. M. Vollebergh[1], Roselind Lieb[3,4], Katja Beesdo-Baum[3], Hans-Ullrich Wittchen[3,5], and Jim van Os[*,2,6]

[1]Department of Interdisciplinary Social Science, University of Utrecht, 3508 TC Utrecht, The Netherlands; [2]Department of Psychiatry and Psychology, School of Mental Health and Neuroscience, Maastricht University Medical Center, PO Box 616 (DRT 10), 6200 MD Maastricht, The Netherlands; [3]Clinical Psychology and Epidemiology Unit, Max Planck Institute of Psychiatry, Munich, Germany; [4]Department of Epidemiology and Health Psychology, Institute of Psychology, University of Basel, Basel, Switzerland; [5]Institute of Clinical Psychology and Psychotherapy, Technical University Dresden, Dresden, Germany; [6]Department of Psychosis Studies, King's College London, King's Health Partners, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

*To whom correspondence should be addressed; tel: +31-43-3875443, fax: +31-43-3875444, e-mail: j.vanos@maastrichtuniversity.nl

Background: **It is commonly assumed that there are clear lines of demarcation between anxiety and depressive disorders on the one hand and psychosis on the other. Recent evidence, however, suggests that this principle may be in need of updating.** ***Methods:*** **Depressive and/or anxiety disorders, with no previous history of psychotic disorder, were examined for the presence of psychotic symptoms in a representative community sample of adolescents and young adults (Early Developmental Stages of Psychopathology study; $n = 3021$). Associations and consequences of psychotic symptomatology in the course of these disorders were examined in terms of demographic distribution, illness severity, onset of service use, and risk factors.** ***Results:*** **Around 27% of those with disorders of anxiety and depression displayed one or more psychotic symptoms, vs 14% in those without these disorders (OR 2.23, 95% CI 1.89–2.66, $P < .001$). Presence as compared with nonpresence of psychotic symptomatology was associated with younger age ($P < .0001$), male sex ($P < .0058$), and poorer illness course ($P < .0002$). In addition, there was greater persistence of schizotypal ($P < .0001$) and negative symptoms ($P < .0170$), more observable illness behavior ($P < .0001$), greater likelihood of service use ($P < .0069$), as well as more evidence of familial liability for mental illness ($P < .0100$), exposure to trauma ($P < .0150$), recent and more distant life events ($P < .0006$–$.0244$), cannabis use ($P < .0009$), and any drug use ($P < .0008$).** ***Conclusion:*** **Copresence of psychotic symptomatology in disorders of anxiety and depression is common and a functionally and etiologically highly relevant feature, reinforcing the view that psychopathology is represented by a network or overlapping and reciprocally impacting dimensional liabilities.**

Key words: psychosis/anxiety disorder/depression/comorbidity/epidemiology

Introduction

Affective dysregulation and reality distortion are correlated but separable dimensions of psychopathology.[1] The association is present over the continuum of subclinical and clinical expression of psychopathology, although stronger in the clinical range.[2] Symptoms and syndromes of depression and anxiety[3,4] are present in the majority of patients with schizophrenia, and these affective symptoms may distinguish distinct subgroups within clinical samples of individuals with psychotic illness.[5] Although the combination of affective disorder with superimposed psychotic disorder is considered rare,[6] psychotic symptoms are often reported in patients with affective disorders.[7,8] Interestingly, the great majority of help-seeking individuals meeting ultra–high risk criteria (UHR) for psychotic disorder in fact initially presents with anxiety disorder or major depression,[9–11] and the same is reported in individuals at psychometric risk for psychosis.[12] Epidemiological community and general population studies have furthermore reported strong associations between the subclinical expression of affective and psychotic symptoms.[13,14]

Thus, affective dysregulation (anxiety and depression) and reality distortion are coexpressed across the range of subclinical and clinical expression. In part, this may be considered the result of mental states that causally impact on each other, eg, affective dysregulation giving rise to psychotic symptoms.[15–17] In addition, genetic studies

have suggested familial links between affective and psychotic disorders[18,19] as well as between schizophrenia and a range of other mental disorders in the nonpsychotic spectrum,[20] suggesting shared liabilities. Furthermore, dimensions of affective and psychotic pathology are associated with similar risk factors,[19,21] although quantitative differences exist in strength of association. There is also evidence of shared underlying endophenotypes such as alterations in cognition,[19,22] as well as social and emotional functioning.[6,19] Additional support for a common factor underlying both affective and psychotic pathology, or for reciprocal causal influence, comes from longitudinal studies showing that subclinical psychotic experiences predict not only later onset of psychotic disorders[23] but also later affective disorders[24], even when the psychotic experiences are not considered clinically relevant.[25]

Evidence suggests that the predictive value of either psychotic or affective symptoms for later psychopathology and worse outcome is highest when they co-occur. One study showed that copresence of subclinical manic and psychotic experiences predicted the development of bipolar disorder more strongly than subclinical manic experiences in isolation.[26] Likewise, the risk of developing a psychotic disorder was higher for individuals with combined expression of subclinical psychotic and affective experiences compared with those with only expression of psychotic experiences.[27] Furthermore, co-occurrence of subclinical psychotic experiences predicted poorer outcome in a community sample of patients with major depressive disorder.[28]

In sum, affective and psychotic phenomena often co-occur, partly on the basis of shared vulnerability and partly on the basis of reciprocal causal influence; co-occurrence predicts poorer course and outcome. These findings have major conceptual and practical implications for diagnosis and treatment. Classificatory principles for mental disorders have been dominated by the nomothetic approach in which criteria relating to symptoms and complaints in patients are assumed to be indicators of an underlying latent diagnostic construct. This approach, however, may not be in agreement with evidence that symptoms in practice form part of overlapping and reciprocally impacting dimensional liabilities that give rise to highly patient-specific admixtures and trajectories.[29] Given the above findings, it may well be that interindividual differences in dimensions that cross the boundaries of traditional disorders have been neglected to the point that important patterns of admixture impacting severity, course, and etiology have been overlooked. A case in point is the group of disorders of anxiety/depression that traditionally are not considered as fundamentally related to expression of psychosis. Instead, expression of psychosis in these disorders is reserved for the definition of rare cases where psychotic symptoms are dominant and clinically severe (as in the case of major depression with psychotic features). However, given the above suggestion of substantial shared vulnerability, shared expression, and reciprocal impact between affective dysregulation and reality distortion, the following questions suggest themselves: (1) how frequent is the expression of psychotic experiences in broadly defined disorders of anxiety and depression? and (2) does the occurrence of psychotic symptoms matter in terms of demography, onset, severity, and etiology?

Methods

Sample

Data from the Early Developmental Stages of Psychopathology (EDSP) study were used. The EDSP study collected data on prevalence, incidence, risk factors, comorbidity, and course of mental disorders in a representative general population sample of adolescents and young adults. Detailed descriptions of the study, sampling methods, instruments, and procedures can be found elsewhere.[30–32] The study was approved by the standing ethics committee. The baseline sample was drawn from population registry offices of Munich and its 29 counties in 1994. This sample was drawn to mirror the distribution of individuals expected to be 14–24 years of age at the time of the baseline (T0) interview in 1995.

The EDSP study was designed as a prospective, longitudinal study consisting of 4 data waves: baseline (T0) and 3 follow-up waves at an average of, respectively, 1.6 (T0–T1, SD 0.2), 3.5 (T0–T2, SD 0.3), and 8.4 (T0–T3, SD 0.7) years after T0. The younger participants (14–17 y) were assessed 4 times and subjects aged 18–24 years only 3 times. For the current analyses, data from the waves with all participants were used (T0, T2, and T3).

Instruments

Psychopathology. Symptoms, syndromes, and disorders were assessed with the computer-assisted version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI),[33] an updated and expanded version of the WHO's CIDI version 1.2 (WHO 1990). The DIA-X/M-CIDI is a comprehensive, fully standardized, diagnostic interview, addressing symptoms, syndromes, and diagnoses of a wide range of mental disorders in accordance with definitions and criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and *International Classification of Diseases, Tenth Edition*. The M-CIDI has been shown to be both reliable and valid. Interviews were conducted by fully trained and experienced psychologists, who were allowed to probe with follow-up questions, which is particularly relevant for the assessment of psychotic symptoms because these are sensitive to false-positive ratings. The EDSP covers a total observation period of up to 10 years. At T0 (baseline), the lifetime version of

the DIA-X/M-CIDI was used; for subsequent waves, the respective DIA-X/M-CIDI interval versions were used. Based on the relevant anxiety disorder and depression sections, dichotomous variables were constructed representing whether an individual had received (1) or had not received (0) a diagnosis of, respectively, a major depressive disorder or any anxiety disorder (includes panic disorder, General Anxiety Disorder [GAD], agoraphobia, specific phobias, and social anxiety disorder, posttraumatic stress disorder [PTSD], and Obsessive Compulsive Disorder [OCD]). The course of disorders of anxiety/depression was measured as the number of times an individual had received any diagnosis in these sections at each wave, at T0, T2, and T3 (range 0–3). Thus, a score of 3 indicates the presence of any anxiety and depressive disorder at all 3 time points. The G-section of the interview on psychotic symptoms and their clinical relevance were only collected at T2 (lifetime version) and T3 (interval version). Presence of positive psychotic symptoms was broadly defined as any rating of ''present'' on any of the 20 core psychosis items, as described previously.[34] Based on the CIDI measures described above, a 3-level variable was constructed indicating whether an individual had (0) no affective (ie, major depressive disorder or any anxiety) disorder and no CIDI psychotic symptoms (the reference group), (1) an affective disorder but no CIDI psychotic symptoms, or (2) an affective disorder and CIDI psychotic symptoms at either T2 or T3. This variable effectively expressed lifetime coexpression of the behavioral liability to psychosis in individuals with major depressive disorder or any anxiety disorder and is hereafter referred to as ''disorders of anxiety/depression.'' Individuals with a diagnosis of psychotic disorder at T2 or T3 ($N = 21$) or bipolar disorder (bipolar I or bipolar II) at any time point ($N = 90$) were excluded from analysis, as otherwise any differences between disorders of anxiety/depression with and without psychotic symptoms would be confounded by psychotic disorder.

Suicidal ideation was addressed with CIDI items rating whether the participant had ever had thoughts about suicide, conforming to previous work.[35] Item ratings were summed over the 3 assessments (range of possible values for each: 0–3).

Negative symptoms were coded as present when the interviewer rated as present item X11 (on flat emotions) and/or X12 (on inadequate communication), in line with previous analyses in this sample.[34] Persistence of negative symptoms was calculated by scoring whether any negative symptom was present never (0) or at 1 (1), 2 (2), or all (3) time points, as described previously.

The Symptom Checklist-90-R (SCL-90-R), a reliable and valid screening instrument for a range of symptoms occurring in the last week, was also administered at all time points. The SCL-90 subscales on psychoticism and paranoid ideation, which rate a broader psychosis phenotype indexing the personality—or schizotypal—dimension of psychosis, were summed to create an SCL-schizotypy score at each time point. Persistence of schizotypy expression was subsequently calculated by scoring whether an individual was in the highest 10% of SCL-schizotypy scores never (0) or at 1 (1), 2 (2), or all (3) time points.[36] Because this schizotypy persistence score was based on the SCL-90-R and not on the CIDI, it could be used to compare anxiety/depression groups with and without CIDI psychotic symptoms.

Clinical Relevance. Help-Seeking Behavior In line with previous analyses reported elsewhere,[36] help-seeking behavior was defined as general help-seeking behavior, which was broadly defined as having visited any mental health institution ever for any mental health problem (based on the Q-section of the M-CIDI).

Caseness Based on the X16 M-CIDI item, a variable indicating ''caseness'' was constructed, reflecting the interviewer's opinion on clinical evidence of mental illness in the participant, scored as not noticeable (0), slightly noticeable (1), clearly noticeable (2), and very ill (3). Conforming to previous work,[36] a dichotomous variable was made based on this item indicating presence of clearly noticeable level of mental disorder (defined as score >1).

Psychiatric Medication Use As part of a module assessing mental health treatments, participants were shown a list of different types of medication and were asked to endorse those they had been given for any psychopathological or psychosomatic problem. The acknowledgment of any psychiatric medication other than antipsychotic medication at T2 and T3 was rated and used as a binary variable in the analyses.

Risk Factors. Substance Use Substance use from any drug or nonprescribed medication was assessed with the L-section of the M-CIDI, assessed at all 3 time points. Conforming to previous work,[37] 2 variables indexing substance use were defined dichotomously as use of (1) any substance and (2) cannabis more than 5 times ever at each time point.

Trauma Self-reported lifetime exposure to trauma was assessed using the N-section of the M-CIDI on trauma and PTSD comprising 9 groups of specific traumatic events (presented by a respondent list) such as ''experienced physical threat,'' ''experienced serious accident,'' or ''being sexually abused as a child.'' Consistent with earlier analyses,[38] positive responses to any of the events were coded as ''self-reported trauma.''

Recent Life Events Recent life events were assessed at T2 with the Munich Interview for the Assessment of Life Events and Conditions (Münchner Ereignis Liste); a reliable 3-step interview assessing recent life events. For each of the 4 years over the period 1995–1998, the total sum of positive and negative life events was calculated.

Urbanicity Consistent with previous work,[39] urbanicity was defined as living in the urban region of the

German city of Munich vs the surrounding areas of Munich. The urban area, thus defined, had a population density of 4061 persons per square mile; for the rural area, this was 553 persons per square mile.

Familial History of Help Seeking The item P8 of the T0 M-CIDI, rating the proband's report on whether any of the proband's family members had ever sought help for emotional or mental problems, was used as a proxy for familial liability for mental disorder.

Analyses

All analyses were carried out with STATA 11.0. Using the MLOGIT command, multinomial logistic regression was used to predict the 3-level outcome variable of disorders of anxiety/depression with/without psychotic symptoms. Given the fact that this outcome was measured twice (lifetime at T2 and interval T2–T3 at T3), data were analyzed in the "long format," each individual contributing 2 observations (T2 and T3) for analysis, conform previous work.[35,36] In order to correct for the clustering of multiple observations within subjects, cluster-robust standard errors were computed using the CLUSTER option in the MLOGIT module in STATA. Individuals without disorders of anxiety/depression and without psychotic symptoms were the reference group. Presence of disorders of anxiety/depression with and without psychotic symptoms was predicted by (1) demographic variables (age, gender, and education), (2) course and severity variables (course of disorders of anxiety/depression, persistence of both schizotypy expression, negative symptoms, and suicidal thoughts), (3) variables relevant for onset of professional help (help-seeking behavior and caseness), and (4) risk factors (family history of mental disorder, trauma, life events, substance use, and urbanicity). All analyses were a priori adjusted for age, sex, and education. OR for disorders of anxiety/depression with and without psychotic symptoms were compared by Wald test using the postestimation TEST command in STATA.

Risk Set. The risk set for analysis were individuals at T2 and T3 who (1) had no diagnosis of bipolar disorder or psychotic disorder, (2) had a diagnosis of disorders of anxiety/depression as defined above, and (3) did not present with psychotic symptoms in the absence of disorders of anxiety/depression as defined above. The reference group consisted of individuals who had neither psychotic/bipolar disorder nor anxiety/depression. This yielded a total risk set of 2118 individuals at T2 and 2027 individuals at T3.

Sensitivity Analysis. A planned sensitivity analysis was carried out excluding individuals with lifetime comorbid anxiety disorder and depressive disorder, sensitively using measures at T0, T2, and T3, in order to examine to what degree any differences between individuals with disorders of anxiety/depression with and without psychotic symptoms was mediated by comorbidity of anxiety and depression, which is associated with greater indices of illness severity and poorer prognosis.[40]

Results

Descriptives

Before exclusion of individuals with bipolar disorder and psychotic disorder, the number of eligible individuals at T0 was $N = 3021$, at T2 $N = 2548$ (84%), and at T3 $N = 2210$ (73%). Of all individuals with disorders of anxiety/depression, as defined for the purpose of this study, 27% also reported psychotic symptoms at any time point (36% at T2 and 19% at T3), vs 14% in those without (OR 2.23, 95% CI 1.89–2.66, $P < .001$)

Associations of Demographics, Severity, Risk Factors, and Onset of Professional Help With Disorders of Anxiety/Depression With/Without Psychotic Symptoms

Analyses in the risk set as defined above (described in table 1) revealed that participants with a disorder of anxiety/depression with psychotic symptoms, compared with those without psychotic symptoms, were more likely to be male and younger (table 2). Lower education differentiated between disorders of anxiety/depression with and without psychotic symptoms, the former group having lower educational attainment. Measures of severity (persistence of both schizotypal and negative psychotic symptoms, suicidal ideation over T0–T3) and course (number of times diagnosed with disorders of anxiety/depression over T0–T3) were associated with both affective conditions but more strongly with disorders of anxiety/depression with psychotic symptoms. The same was found for associations with variables relevant for onset of professional help and risk factors: these variables were significantly associated with presence of disorders of anxiety/depression with and without psychotic symptoms but more strongly with disorders of anxiety/depression with psychotic symptoms.

The sensitivity analyses showed that results were largely robust to exclusion of comorbid anxiety and depression states from the analyses (see last column table 2). Generally, all patterns remained similar, ie, quantitative differences were found between disorders of anxiety/depression with and without psychotic symptoms, with the strongest associations found for individuals with additional psychotic symptoms. Three predictors no longer discriminated significantly between the 2 groups, namely, use of cannabis ($P < .0622$), help seeking ($P < .208$), and life events that had occurred in the second year after baseline assessment ($P < .068$). However, the results still showed a trend toward quantitative differences and still

Table 1. Descriptives of Risk Set at T2 and T3, as well as of Entire Population at T2 and T3

	Risk Set		Total Sample	
	T2	T3	T2	T3
N total	2118	2027	2548	2210
Mean age (SD)	21.8 (3.4)	26.6 (3.5)	21.7 (3.4)	26.6 (3.5)
% Females (%)	49.8	49.7	49.1	48.6
Level of education				
Low	264 (12%)	239 (12%)	323 (13%)	271 (12%)
Medium	647 (31%)	582 (29%)	769 (30%)	647 (30%)
High	1207 (57%)	1206 (59%)	1456 (57%)	1292 (58%)
Major depressive episode				
Not present	1905 (90%)	1791 (88%)	2296 (90%)	1972 (89%)
Present	213 (10%)	236 (12%)	233 (9%)	238 (11%)
Missing	0	0	19 (1%)	0
Anxiety disorder				
Not present	1756 (83%)	1649 (81%)	2168 (85%)	1825 (83%)
Present	362 (17%)	378 (19%)	380 (15%)	385 (17%)
Missing	0	0	0	0
Psychotic symptoms				
Not present	1941 (92%)	1930 (95%)	1950 (77%)	1936 (88%)
Present	177 (8%)	97 (5%)	574 (22%)	274 (12%)
Missing	0	0	24 (1%)	0
Disorders of anxiety/depression and psychotic symptoms				
Neither	1630 (77%)	1509 (74%)	1630 (64%)	1509 (69%)
Disorders of anxiety/depression without psychotic symptoms	311 (15%)	421 (21%)	311 (12%)	421 (19%)
Disorders of anxiety/depression with psychotic symptoms	177 (8%)	97 (5%)	177 (7%)	97 (4%)
Missing			430 (17%)	183 (8%)
Negative symptoms				
Not present	1850 (87%)	1785 (88%)	2223 (87%)	1938 (88%)
Present	268 (13%)	240 (12%)	325 (13%)	270 (12%)
Missing	0	2 (0.1%)	0	2 (0.1%)
Suicidal thoughts				
None	1819 (86%)	1735 (86%)	2192 (86%)	1883 (85%)
At 1 time point	245 (12%)	236 (12%)	293 (12%)	264 (12%)
At 2 time points	46 (2%)	47 (2%)	54 (2%)	54 (2%)
At 3 time points	8 (0.4%)	9 (0.4%)	9 (0.4%)	9 (1%)
General help seeking				
No	1923 (91%)	1717 (85%)	2314 (91%)	1870 (85%)
Yes	195 (9%)	310 (15%)	233 (9%)	340 (15%)
Missing	0	0	1 (0.04%)	0
Psychiatric medication use (nonpsychotic)				
No	2114 (100%)	2013 (99%)	2539 (100%)	2194 (99%)
Yes	4 (0.2%)	14 (1%)	8 (0.3%)	16 (1%)
Missing	0	0	1 (0.1%)	0
Any drug use >5 times				
No	1690 (80%)	1482 (73%)	1979 (77%)	1600 (72%)
Yes	412 (19%)	526 (26%)	529 (21%)	589 (27%)
Missing	16 (1%)	19 (1%)	40 (2%)	21 (1%)
Cannabis use >5 times				
No	1679 (79%)	1474 (73%)	1966 (77%)	1592 (72%)
Yes	404 (19%)	512 (25%)	519 (20%)	574 (26%)
Missing	35 (2%)	41 (2%)	63 (3%)	44 (2%)

Table 1. Continued

	Risk Set		Total Sample	
	T2	T3	T2	T3
Trauma				
No	1715 (81%)	1641 (81%)	2052 (81%)	1783 (81%)
Yes	403 (19%)	386 (19%)	496 (19%)	427 (19%)
Mean (SD) number of life events				
Recent life events (T0)	4.18 (3.03)	3.88 (3.13)	4.22 (3.08)	3.91 (3.15)
Recent life events (T0 + 1 y)	5.28 (3.38)	5.01 (3.58)	5.38 (3.43)	5.06 (3.62)
Recent life events (T0 + 2 y)	6.85 (3.66)	6.35 (3.92)	6.91 (3.68)	6.42 (3.94)
Recent life events (T0 + 3 y)	6.84 (3.73)	6.34 (3.96)	6.90 (3.73)	6.41 (3.98)
Urbanicity				
Urban	1488 (70%)	1427 (70%)	1796 (71%)	1558 (71%)
Rural	630 (30%)	600 (30%)	752 (29%)	652 (29%)
Proband's report of familial psychopathology				
No	1684 (80%)	1596 (79%)	2018 (79%)	1744 (79%)
Yes	421 (20%)	421 (21%)	516 (20%)	453 (20%)
Missing	13 (0.6%)	10 (0.5%)	14 (1%)	13 (1%)

displayed the strongest associations for individuals with additional psychotic symptoms.

Discussion

Findings

Psychotic symptoms were reported in 27% of individuals with a disorder of anxiety/depression in a large sample of adolescents and young adults from the general population. Individuals with a disorder of anxiety/depression were also more likely to report psychotic symptoms than individuals without such a disorder. Both anxiety/depression disorder groups, ie, with and without psychotic symptoms, differed from controls (indicating lack of qualitative differences), but anxiety/depression with psychotic symptoms showed larger effect sizes than anxiety/depression without psychotic symptoms (indicating quantitative differences). Thus, anxiety/depression disorders with and without psychotic symptoms were distinguished quantitatively by indicators of severity, course, onset, and environmental and familial risks. The findings could not be attributed to comorbidity of anxiety and depression per se because the sensitivity analyses showed that the pattern of results was largely robust to exclusion of this comorbidity.

Disorders of Anxiety/Depression With Psychosis: A Prevalent and More Severe Disorder

The present findings confirm earlier work that psychopathological dimensions of affective dysregulation and reality distortion often co-occur.[3,5,14,17] Most research on this co-occurrence was published from the perspective of psychosis research, thus focusing on the additional presence of disorders of anxiety/depression in individuals endorsing psychotic phenomena. However, the present study joins a novel line of research that takes an alternative perspective. Although previous work has shown that psychotic symptoms are common in clinical samples presenting with disorders of anxiety/depression,[7,8] the current study aimed to quantify (1) the prevalence and (2) the consequences of psychotic symptoms in individuals with disorders of anxiety/depression in an epidemiological general population sample.

The findings indicate that the sizeable subgroup of individuals with disorders of anxiety/depression and psychotic symptoms has a more severe condition than those without psychotic symptoms. These findings are in agreement with studies showing that comorbidity of affective and psychotic psychopathology is more severe and of poorer prognosis than disorders without multidimensional admixture.[41] It also validates the interpretation of psychotic symptoms as complicating factors in disorders of anxiety/depression, characterizing a group of individuals with more severe pathology, earlier need for care, and more etiological loading.

The results support a hypothesized continuum of vulnerability between affective dysregulation and reality distortion, in which individuals who are vulnerable for either dimension are also more prone to develop the other.[7,12,43] Our results support this notion by showing that individuals with disorders of anxiety/depression are more prone to develop psychotic symptoms.

Disorders of Anxiety/Depression, Psychotic Symptoms, and UHR Status

Another explanation relevant to these findings is that individuals with disorders of anxiety/depression and psychotic symptoms are in a prodromal stage of psychotic disorder. The rationale for this reasoning is that affective

Table 2. Associations of Demographic, Severity, Clinical Relevance, and Risk Factors With Having Disorders of Anxiety/Depression With and Without Psychotic Symptoms

	No Disorders of Anxiety/Depression and No Psychotic Symptoms	Disorders of Anxiety/Depression Without Psychotic Symptoms	Disorders of Anxiety/Depression With Psychotic Symptoms	Difference Between Disorders of Anxiety/Depression With/Without Psychotic Symptoms	Sensitivity Analysis: Difference Between Disorders of Anxiety/Depression With/Without Psychotic Symptoms Excluding Individuals With Comorbidity of Anxiety and Depression
Demographics		OR (95% CI)	OR (95% CI)	χ^2(df), *P* Value	
Age	[a]	1.05 (1.04–1.08)***	0.96 (0.93–0.99)**	$\chi^2(1) = 40.76$, $P < .0001$	$\chi^2(1) = 30.35$, $P < .0001$
Gender				$\chi^2(1) = 7.62$, $P < .0058$	$\chi^2(1) = 5.57$, $P < .0183$
Male	[a]	[a]	[a]		
Female	[a]	2.47 (2.06–2.96)***	1.61 (1.22–2.13)***		
Education				$\chi^2(1) = 6.04$, $P < .0140$	$\chi^2(1) = 6.43$, $P < .0112$
Low	[a]	[a]	[a]		
Medium	[a]	0.84 (0.62–1.12)	0.77 (0.51–1.17)		
High	[a]	0.74 (0.56–0.98)*	0.48 (0.33–0.71)***		
Linear trend		0.87 (90.77–0.99)*	0.68 (0.60–0.81)***		
Psychopathology					
Persistence of negative symptoms	[a]			$\chi^2(1) = 5.70$, $P < .0170$	$\chi^2(1) = 6.67$, $P < .0098$
No negative symptoms		[a]	[a]		
1 Time point		1.12 (0.88–1.42)	1.54 (1.08–2.21)*		
2 Time points		1.41 (0.86–2.32)	2.76 (1.53–4.95)***		
3 Time points		3.23 (1.15–9.06)*	5.79 (1.38–24.34)*		
Linear trend		1.20 (1.01–1.42)*	1.64 (1.30–2.07)***		
Persistence of schizotypal symptoms	[a]			$\chi^2(1) = 55.14$, $P < .0001$	$\chi^2(1) = 43.57$, $P < .0001$
No schizotypal symptoms		[a]	[a]		
1 Time point		2.53 (1.97–3.24)***	5.28 (3.60–7.75)***		
2 Time points		2.36 (1.53–3.66)***	14.25 (8.91–22.78)***		
3 Time points		7.44 (2.34-23.64)***	63.29 (20.28-197.48)***		
Linear trend		1.95 (1.66–2.29)***	4.15 (3.39–5.08)***		
Course disorders of anxiety/depression	[a]	12.53 (11.13–14.10)***	18.36 (14.89–22.22)***	$\chi^2(1) = 12.64$, $P < .0004$	$\chi^2(1) = 4.15$, $P < .0417$
Suicidal thoughts	[a]	2.30 (1.71–3.38)***	3.02 (2.08–4.38)***	$\chi^2(1) = 3.15$, $P < .0761$	$\chi^2(1) = 1.28$, $P < .2581$
Clinical relevance					
General help seeking	[a]	4.66 (3.73–5.82)***	7.14 (5.28–9.66)***	$\chi^2(1) = 7.29$, $P < .0069$	$\chi^2(1) = 1.61$, $P < .2041$
Psychiatric medication use	[a]	3.99 (1.35–11.76)*	7.46 (1.98–28.15)**	$\chi^2(1) = 1.03$, $P < .3095$	$\chi^2(1) = 0.14$, $P < .7063$
Interviewer impression of "Caseness"	[a]	11.51 (5.84–22.72)***	53.18 (27.53–102.76)***	$\chi^2(1) = 39.06$, $P < .0001$	$\chi^2(1) = 8.85$, $P < .0029$
Risk factors					
Any drug use >5 times	[a]	1.55 (1.25–1.93)***	2.56 (1.93–3.40)***	$\chi^2(1) = 11.28$, $P < .0008$	$\chi^2(1) = 4.64$, $P < .0312$
Cannabis use >5 times	[a]	1.51 (1.22–1.88)***	2.56 (1.93–3.40)***	$\chi^2(1) = 10.99$, $P < .0009$	$\chi^2(1) = 3.48$, $P < .0622$
Trauma assessed at T0	[a]	1.39 (1.12–1.73)**	2.13 (1.55–2.92)***	$\chi^2(1) = 5.92$, $P < .0150$	$\chi^2(1) = 7.30$, $P < .0069$
Recent life events (T0)	[a]	1.00 (0.97–1.03)	1.09 (1.04–1.14)***	$\chi^2(1) = 11.82$, $P < .0006$	$\chi^2(1) = 8.52$, $P < .0035$
Recent life events (T0 + 1 y)	[a]	1.02 (0.99–1.04)	1.08 (1.04–1.12)***	$\chi^2(1) = 7.52$ $P < .0006$	$\chi^2(1) = 4.95$, $P < .0261$
Recent life events (T0 + 2 y)	[a]	1.03 (1.00–1.05)*	1.07 (1.03–1.11)***	$\chi^2(1) = 5.06$, $P < .0244$	$\chi^2(1) = 3.33$, $P < .0682$

Table 2. Continued

	No Disorders of Anxiety/Depression and No Psychotic Symptoms	Disorders of Anxiety/Depression Without Psychotic Symptoms	Disorders of Anxiety/Depression With Psychotic Symptoms	Difference Between Disorders of Anxiety/Depression With/Without Psychotic Symptoms	Sensitivity Analysis: Difference Between Disorders of Anxiety/Depression With/Without Psychotic Symptoms Excluding Individuals With Comorbidity of Anxiety and Depression
Recent life events (T0 + 3 y)	[a]	1.01 (0.99–1.04)	1.08 (1.04–1.12)***	$\chi^2(1) = 9.35$, $P < .0022$	$\chi^2(1) = 5.32$, $P < .0211$
Urbanicity				$\chi^2(1) = 0.59$, $P < .4441$	$\chi^2(1) = 0.70$, $P < .4037$
Rural	[a]	[a]	[a]		
Urban	[a]	1.31 (1.07–1.60)**	1.50 (1.08–2.08)*		
Proband's report of familial psychopathology	[a]	1.10 (1.05–1.16)***	1.23 (1.14–1.33)***	$\chi^2(1) = 7.31$, $P < .0069$	$\chi^2(1) = 7.85$, $P < .0051$

Note: The last column refers to the planned sensitivity analysis—"sensitivity analysis: difference between disorders of anxiety/depression with/without psychotic symptoms excluding individuals with comorbidity of anxiety and depression." *$P < .05$, **$P < .01$, ***$P < .001$. All analyses (except for demographics) were controlled for age, gender, and education. Persistence of negative symptoms: Munich-Composite International Diagnostic Interview (CIDI) negative symptoms present at 1, 2, or 3 time points; persistence of schizotypal symptoms: presence of Symptom Checklist-90-R schizotypal symptoms (different from CIDI measures of psychotic symptoms used to define anxiety/depression with psychotic symptoms) at 1, 2, or 3 time points; course disorders of anxiety/depression: disorders of anxiety/depression present at 1, 2, or 3 time points; suicidal thoughts: presence of suicidal thoughts at 1, 2, or 3 time points; general help seeking: whether participant had visited any mental health institution ever for any mental health problem; psychiatric medication use: use of psychiatric medication other than antipsychotic medication; caseness: interviewer's opinion on clinical evidence of mental illness in the participant; any drug use: use of any drug more than 5 times; cannabis use: use of cannabis more than 5 times; trauma: lifetime assessment of trauma at T0; recent life events: sum of positive and negative life events; proband's report of familial psychopathology: proband's report on whether any of the proband's family members had ever sought help for emotional or mental problems.

[a]Reference group

symptoms (1) form an intrinsic dimension of psychosis,[29] (2) are the most common (and earliest) retrospectively reported prodromal symptoms[6] that may come online earlier than psychotic phenomena that form the core characteristic of UHR status in help-seeking individuals, and (3) predict transition and worse outcome in UHR samples.[11,44] This interpretation, however, is not likely, given (1) the very large number of individuals in the present study reporting both disorders of anxiety/depression and psychotic symptoms, (2) the low prevalence of psychotic disorder in the population, and (3) the low number of individuals within the group at ultra-high risk for psychosis that actually make the transition to psychotic disorder.[44] Conversely, however, it can be considered likely that many of the help-seeking individuals presenting as UHR for psychosis actually represent the group with disorders of anxiety/depression with comorbid psychotic symptoms. In other words, a substantial proportion of help-seeking individuals presenting as UHR may in fact present with disorders of anxiety/depression complicated by psychotic symptoms, which is supported by (1) the observation that the great majority of UHR individuals initially carries a diagnosis of anxiety disorder and/or depression[9–11] and (2) reports that part of this group responds favorable to antidepressant medication.[45] Because disorders of anxiety/depression have traditionally been considered as "nonpsychotic," this explanation has not been considered before.

Diagnostic Implications

Mental disorder nosology is based on the theory that the signs and symptoms associated with mental ill health fluctuate as a function of an underlying latent diagnostic construct. However, disorders in practice do not occur in isolation, be it a combination of affective and psychotic disorder[3] or mental disorder diagnoses in general.[46] The data, in combination with previous work, suggest that psychopathology may be considered as a network of symptom dimensions that reciprocally impact each other over time and are linked as part of a homeostatic mechanism, time, and/or share liability. An approach that possibly can accommodate this type of variation over time is the clinical staging model,[47] in combination with a network model of psychopathology.[48] Thus, reciprocally impacting symptoms sharing degrees of liability may develop across stages of severity and comorbidity.

Methodological Issues

The current results should be interpreted in light of the strengths and limitations of the study. A major strength of the study was that it addressed the copresence of disorders of anxiety/depression and psychotic symptoms, assessed by psychologists who were allowed to probe with clinical questioning, in a large, representative population study that was followed over an extended period. However, the relatively long follow-up period with only 3 assessments also limits the possibilities of constructing dynamic, microlevel models of the development of reciprocally impacting domains of psychopathology. Second, even though psychotic symptoms were assessed by psychologists using clinical questioning, false-positive ratings are likely to have occurred. However, the effect of this would be conservative rather than to give rise to spurious associations. Furthermore, even "false-positive" ratings of positive psychotic symptoms have been shown to be predictive of later (psychotic and affective) pathology[25] and therefore are important predictors to include. Third, some of the risk factors that were investigated should be interpreted carefully. For example, the variable reflecting caseness was assigned by the same interviewer enquiring about psychopathology and therefore may be biased. Finally, some of the assessments of the exposure variables may have been biased because individuals who are more severely ill may report greater degree of exposure to, eg, childhood trauma or life events.

Funding

European Union (EU) Interreg IVb project "Health and Demographic Changes" (30972507N); European Community's Seventh Framework Program (HEALTH-F2-2009-241909, Project EU-GEI); German Federal Ministry of Education and Research (BMBF) (01EB9405/6, 01EB9910/6, EB10106200, 01EB0140, 01EB0440); Deutsche Forschungsgemeinschaft (LA1148/1-1, WI2246/7-1, WI709/8-1).

Acknowledgments

This work is part of the EDSP study. Core staff members of the EDSP group are Dr Kirsten von Sydow, Dr Gabriele Lachner, Dr Axel Perkonigg, Dr Peter Schuster, Dipl.-Stat. Michael Höfler, Dipl.-Psych. Holger Sonntag, Dipl.-Psych. Tanja Brückl, Dipl.-Pych. Elzbieta Garczynski, Dr Barbara Isensee, Dipl.-Psych. Agnes Nocon, Dr Chris Nelson, Dipl.-Inf. Hildegard Pfister, Dr Victoria Reed, Dipl.-Soz. Barbara Spiegel, Dipl.-Psych. Andrea Schreier, Dr Ursula wunderlich, Dr Petra Zimmermann, Dipl.-Psych. Datja Beesdo, and Dipl.-Psych. Antje Bitner. Scientific advisors are Dr Jules Angst (Zurich), Dr Jürgen Margraf (Basel), Dr Günther Esser (Potsdam), Dr Kathleen Merikangas (National Institute of Mental Health [NIMH], Bethesda), Dr Ron Kessler (Harvard, Boston), and Dr Jim van Os (Maastricht). The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Kotov R, Chang SW, Fochtmann LJ, et al. Schizophrenia in the internalizing-externalizing framework: a third dimension? *Schizophr Bull*. 2011;37:1168–1178.

2. Krabbendam L, Myin-Germeys I, de Graaf R, et al. Dimensions of depression, mania and psychosis in the general population. *Psychol Med*. 2004;34:1177–1186.
3. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull*. 2009; 35:383–402.
4. Huppert JD, Smith TE. Anxiety and schizophrenia: the interaction of subtypes of anxiety and psychotic symptoms. *CNS Spectrums*. 2005;10:721–731.
5. Boks MPM, Leask S, Vermunt JK, Kahn RS. The structure of psychosis revisited: the role of mood symptoms. *Schizophr Res*. 2007;93:178–185.
6. Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M. The early course of schizophrenia and depression. *Eur Arch Psychiatry Clin Neurosci*. 2005;255:167–173.
7. Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, van Os J. How psychotic are individuals with non-psychotic disorders? *Soc Psychiatry Psychiatr Epidemiol*. 2003;38: 149–154.
8. Olfson M, Lewis-Fernández R, Weissman MM, et al. Psychotic symptoms in an urban general medicine practice. *Am J Psychiatry*. 2002;159:1412–1419.
9. Addington J, Cornblatt BA, Candenhead KS, et al. At clinical high risk for psychosis: outcome for nonconverters. *Am J Psychiatry*. 2011;168:800–805.
10. Velthorst E, Nieman DH, Becker HE, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. *Schizophr Res*. 2009;109:60–65.
11. Yung AR, Phillips L, Yuen H, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res*. 2004;67:131–142.
12. Verdoux H, van Os J, Maurice-Tison S, Gay B, Salamon R, Bourgeois M-L. Increased occurrence of depression in psychosis-prone subjects: a follow-up study in primary care settings. *Compr Psychiatry*. 1999;40:462–468.
13. Armando M, Nelson B, Yung AR, et al. Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. *Schizophr Res*. 2010;119:258–265.
14. Varghese D, Scott J, Welham J, et al. Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophr Bull*. 2011;37: 389–393.
15. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med*. 2001;31:189–195.
16. Freeman D, Garety PA. Connecting neurosis and psychosis: the direct influence of emotion on delusions and hallucinations. *Behav Res Ther*. 2003;41:923–947.
17. van Rossum I, Dominguez M, Lieb R, Wittchen HU, van Os J. Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. *Schizophr Bull*. 2011;37:561–571.
18. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373: 234–239.
19. Weiser M, van Os J, Davidson M. Time for a shift in focus in schizophrenia: from narrow phenotypes to broad endophenotypes. *Br J Psychiatry*. 2005;187:203–205.
20. Mortsenen PB, Pedersen MG, Pedersen CB. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychol Med*. 2010;40: 201–210.
21. Breetvelt EJ, Boks MPM, Numans ME, et al. Schizophrenia risk factors constitute general risk factors for psychiatric symptoms in the population. *Schizophr Res*. 2010;120:184–190.
22. Bora E, Yucel M, Pantelis C. Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond. *Schizophr Bull*. 2010;36:36–42.
23. Chapman LJ, Chapman JP, Kwapil TR, Eckblad M, Zinser MC. Putatively psychosis-prone subjects 10 years later. *J Abnorm Psychol*. 1994;103:171–183.
24. Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Gamma A, Angst J. Sub-clinical psychosis symptoms in young adults are risk factors for subsequent disorders of anxiety/depression. *Schizophr Res*. 2011;131:18–23.
25. van Nierop M, van Os J, Gunther N, et al. Phenotypically continuous with clinical psychosis, discontinuous in need for care: evidence for an extended psychosis phenotype. *Schizophr Bull*. 2012;38:231–238.
26. Kaymaz N, van Os J, de Graaf R, ten Have M, Nolen W, Krabbendam L. The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder. *J Affect Disorders*. 2007;98:55–64.
27. Krabbendam L, Myin-Germeys I, Hanssen M. Development of depressed mood predicts onset of psychotic disorder in individuals who report hallucinatory experiences. *Br J Clin Psychol*. 2005;44:113–125.
28. Perlis RH, Uher R, Ostacher M. Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Arch Gen Psychiatry*. 2011;68:351–360.
29. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010;468:203–212.
30. Lieb R, Isensee B, Von Sydow K, Wittchen H. The early developmental stages of psychopathology study (EDSP): a methodological update. *Eur Addict Res*. 2000;6:170–182.
31. Wittchen H, Perkonigg A, Lachner G, Nelson C. Early developmental stages of psychopathology study (EDSP): objectives and design. *Eur Addict Res*. 1998;4:18–27.
32. Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of Generalized Anxiety Disorder. *Arch Gen Psychiatry*. 2010;67:47–57.
33. Wittchen H, Pfister H. DIA-X-Interviews: Manual fur Screening-Verfahren und Interview; Interviewheft Langsschnittuntersuchung (DIA-X-Lifetime); Enganzungsheft (DIA-X-Lifetime); Interviewheft Querschnittsuntersuchung (DIA-X-Monatsversion); Erganzungsheft (DIA-X-12 Montasversion); PC-Programm zur Durchfuhrung der Interviews (Langsund Querschnittsuntersuchung). Ausertungsprogramm. Frankfurt, Germany: Swets & Zeiltinger; 1997.
34. Dominguez M, Saka MC, Lieb R, Wittchen H-U, van Os J. Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. *Am J Psychiatry*. 2010;167:1075–1082.
35. Smeets F, Lataster T, Dominguez M. Evidence that onset of psychosis in the population reflects early hallucinatory experiences that through environmental risks and affective dysregulation become complicated by delusions. [published online ahead of print October 28, 2010]. *Schizophr Bull*. doi:10.1093/schbul/sbq117.
36. Dominguez M, Wichers M, Lieb R, Wittchen H-U, van Os J. Evidence that onset of clinical psychosis is an outcome of

progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophr Bull*. 2011;37:84–93.

37. Henquet C, Krabbendam L, Spauwen J. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ*. 2005;30:11–14.
38. Spauwen J, Krabbendam L, Lieb R, Wittchen H-U, van Os J. Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *Br J Psychiatry*. 2006;188:527–533.
39. Spauwen J, Krabbendam L, Lieb R, Wittchen HU, van Os J. Does urbanicity shift the population expression of psychosis? *J Psychiatr Res*. 2004;38:613–618.
40. Penninx BWJH, Nolen WA, Lamers F. Two-year course of depressive and anxiety disorders: results from The Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord*. 2011;133:76–85.
41. Saarni SI, Viertio S, Perala J, Koskinen S, Lonnqvist J, Suvisaari J. Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. *Br J Psychiatry*. 2010;197:386–394.
42. Green C, Garety P, Freeman D. Content and affect in persecutory delusions. *Br J Clin Psychol*. 2006;45:561–577.
43. Lin A, Wood SJ, Nelson B. Neurocognitive predictors of functional outcome nine to 13 years after identification as ultrahigh risk for psychosis. *Schizophr Res*. 2011;132:1–7.
44. Yung AR, Yuen HP, Berger G. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull*. 2007;33:673–681.
45. Cornblatt B, Lencz Y, Obuchowski M. The schizophrenia prodrome: treatment and high-risk perspectives. *Schizophr Res*. 2002;54:177–186.
46. Kessler RC, Ormel J, Petukhova M. Development of lifetime comorbidity in the world health organization world mental health surveys. *Arch Gen Psychiatry*. 2011;68:90–100.
47. McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *MJA*. 2007;187:S40–S42.
48. Borsboom D, Cramer AOJ, Schmittmann VD, Epskamp S, Waldorp LJ. The small world of psychopathology. *PLoS ONE*. 2011;6:e27407.