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# Comparing the prodrome of schizophrenia-spectrum psychoses and affective disorders with and without psychotic features

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ABSTRACT

*Objective:* Following encouraging results in the early detection of psychotic disorders, interest in the early detection of affective, especially bipolar disorders, has recently been renewed. However, the differentiation between affective disorders with and without psychotic features is often missing, although it has been suggested that affective disorders with psychotic features may be distinct from those without psychotic features and closely linked to non-affective psychoses.
*Methods:* We compared the prodromal symptoms of patients who had sought help at an early detection center; had been assessed at baseline with the Structured Interview for Prodromal Syndromes (SIPS); and who, within 53 months on average, developed schizophrenia-spectrum psychosis (pre-SCZ; $n=51$), affective disorder with psychotic features (pre-AD-P; $n=7$), or affective disorder without psychotic features (pre-AD-noP; $n=16$).
*Results:* While pre-SCZ scored slightly higher on most positive symptoms than pre-AD, pre-AD-P and pre-SCZ scored comparably across the SIPS; moreover, pre-AD-noP and pre-SCZ differed on most subscales and items, particularly on the positive and negative dimensions. Furthermore, pre-AD-P scored higher on positive symptoms than pre-AD-noP.
*Conclusions:* Our results suggest that, in the early detection of affective disorders, those that might take on a psychotic form and those with a non-psychotic course need to be considered separately. While the current at-risk criteria for psychosis function well in detecting those with a psychotic course, those with a non-psychotic course would benefit from the development and evaluation of new at-risk criteria and new early detection instruments.


## 1. Introduction

Following first promising results in the early detection of psychosis, interest in the early detection of affective, especially bipolar, disorders has gained new momentum (Cuijpers, 2011; Howes et al., 2011; Bechdolf et al., 2012). This interest has arisen because most individuals with depressive and bipolar disorder also experience prolonged subsyndromal symptoms prior to disorder development (Murphy et al., 1989; Fava and Kellner, 1991; Howes et al., 2011). Alike psychotic disorders, however, affective disorders are a heterogeneous group of disorders not only distinguished by unipolar and bipolar courses but also by psychotic and non-psychotic clinical courses. The occurrence of psychotic features in affective disorders (Gaudiano et al., 2009) and the fact that the affective domain is frequently impacted in non-affective psychosis (Cotton et al., 2012) nourish the ongoing debate about the differentiation between affective and non-affective psychotic disorders and the concept of a unitary psychosis (van Os et al., 2000; Angst, 2002; Peralta and Cuesta, 2005; Kumbier and Herpertz, 2010; Reininghaus et al., 2012). Further, data from family studies suggest a relation between schizophrenia and affective disorders with psychotic features, particularly mood-incongruent psychotic features, but not between schizophrenia and affective disorders without psychotic features (Kendler et al., 1993). However, data from birth cohort studies suggest that schizophrenia and affective disorders share many developmental precursors (Jones & Tarrant, 1999).

Recently, the first attempts to define at-risk states of bipolar disorder prior to the first (hypo-) manic episode were made. Alike the "ultra-high risk" (UHR) criteria of psychosis (Phillips et al., 2000), these at-risk criteria mainly target subthreshold forms of the disorder (Correll et al., 2007b; Bechdolf et al., 2012). Furthermore, Olvet et al. (2010) compared clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome within a sample at clinical high risk (CHR) for schizophrenia-spectrum psychosis. In this sample, 29 patients converted to schizophrenia-spectrum psychoses (pre-SCZ) and

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8 to bipolar disorders (pre-BP). At initial presentation, pre-SCZ and pre-BP differed neither on the SIPS positive symptoms total score nor in global functioning or on a composite global neurocognitive score. Moreover, the sociodemographic characteristics were comparable between both groups. The authors concluded that the bipolar prodrome and the schizophrenia-spectrum prodrome may be indistinguishable based on clinical and neurocognitive measures used in at-risk research for psychoses. Yet, it is noteworthy that 5 of the 8 pre-BP in this study reported psychotic features at the time of their first manic episode; this 63% rate of bipolar disorder with psychotic features might account for the missing clinical differences between the two groups. However, such a presumed difference between psychotic and non-psychotic forms may not be restricted to bipolar disorders but may also apply to severe depressive disorders, i.e., to affective disorders in general.

Therefore, we aimed to compare the clinical features, particularly the UHR criteria, of psychosis between 51 pre-SCZ and 23 patients who later developed severe affective disorder (pre-AD) with special consideration of differences between the 7 pre-AD with (pre-AD-P) and the 16 pre-AD without psychotic features (pre-AD-noP). Given that pre-AD-P were in the minority (30%), we expected more clinical differences between the pre-SCZ and pre-AD than reported by Olvet et al. (2010). Furthermore, we expected to find differences between pre-AD-P and pre-AD-noP, particularly regarding attenuated psychotic symptoms, and expected a great similarity in the clinical picture of pre-SCZ and pre-AD-P but not pre-AD-noP.

## 2. Methods

Data were sourced from patients who sought help for mental problems at the Early Recognition and Intervention Centre (FETZ) in Cologne between 1998 and 2003 (Schultze-Lutter et al., 2009) and participated in a naturalistic follow-up study. On average, patients were followed 53 months after baseline (SD = 21; MD = 53; 12–124).

Patients were included if they had met attenuated negative symptoms (ANS) or attenuated positive symptoms (APS) according to the CHR criteria (Cornblatt et al., 2003) at baseline (i.e., a score of at least moderate on any negative symptom or of moderate to severe on any positive symptom on the Structured Interview for Prodromal Syndromes; SIPS 3.0, McGlashan et al., 2001). Patients were excluded if, at baseline, they scored "severe and psychotic" on any SIPS positive symptom ($n = 20$ pre-SCZ), i.e., reported Brief Limited Intermittent Psychotic Symptoms (BLIPS) or met DSM-IV criteria for an Axis I schizophrenia-spectrum psychosis disorder or major depressive disorder with psychotic features/BLIPS. Further exclusion criteria were bipolar spectrum disorder, medical or neurological disorders that could affect brain functioning, drug or alcohol dependence within the past 6 months, or an estimated IQ below 70 at baseline. Moreover, patients with a conversion to schizoaffective disorder ($n = 1$) or to drug-induced psychosis ($n = 4$) at follow-up were excluded to avoid dilution of results by including an "in-between" schizoaffective group or a group with a possibly different symptom etiology. All patients provided written informed consent for follow-up assessments and use of the clinical baseline data.

Seventy-four patients met the above inclusion and exclusion requirements and later converted to an affective disorder or schizophrenia-spectrum psychosis. Fifty-one converted to a schizophrenia-spectrum psychosis (pre-SCZ; schizophrenia: $n = 46$; schizophreniform disorder: $n = 3$; delusional disorder: $n = 2$) and 23 to an affective disorder (bipolar I disorder: $n = 4$, 2 with psychotic features; bipolar II disorder: $n = 3$, 1 with psychotic features; bipolar NOS: $n = 3$, 1 with psychotic features; major depressive episode: $n = 11$, 3 with psychotic features; those without psychotic features had 3 episodes on average).

All patients were assessed at baseline with the SIPS. SIPS 2.1 was used until 2001 and SIPS 3.0, thereafter. The Positive Syndrome section (items P1 to P5) of these two versions has generally remained unchanged. Scores of the 6 negative (items N1 to N6), 4 disorganized (items D1 to D4), and 4 general SIPS items (items G1 to G4) are only somewhat comparable because the severity rating was done according to item frequency in version 2.1 and to symptom- and behavior-related anchor points in version 3.0. However, this change in severity rating affects groups equally (total group: 71% of pre-SCZ and 82% of pre-AD were assessed in 2001 or later: $\chi^2_{(1)} = 1.200$, $p = .273$; pre-AD group: 86% of pre-AD-P and 81% of pre-AD-noP were assessed in 2001 or later: Fisher's test = 0.068, $p = 1.0$). Furthermore, year of assessment (until or after 2000) correlated only marginally with the sum scores of the negative, disorganized, and general SIPS sections and the presence of ANS (total group: Kendall's tau $\leq -.218$, $p \geq .252$; pre-AD group: Kendall's tau $\leq -.167$, $p \geq .088$). Thus, assuming little if any effect of this scoring change on group comparisons, we also compared the negative, disorganized, and general SIPS sections. Moreover, the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992) that measures social and occupational functioning independent from symptoms and psychological functioning was used as a global measure of functioning ranging from 100 (highest) to 0 (lowest). At follow-up, an intervening conversion to any psychosis or affective disorder was assessed with the respective sections of the German version of the Structured Clinical Interview for DSM-IV (SCID-I; Wittchen et al., 1997).

Group differences in frequencies were calculated using $\chi^2$-tests and, in the small group of pre-AD, Fisher's exact test. Group differences in the ordinal-scaled SIPS data and SOFAS were analyzed using the Mann–Whitney *U*-test with the exact significance option to account for small sample sizes. For reasons of sample size, even clinical meaningful differences between pre-AD-P and pre-AD-noP were not expected to reach significance even on the descriptive level without adjustment for multiple testing. The effect size was therefore chosen as the main statistical descriptor. The calculated effect size was Rosenthal's r for the Mann–Whitney *U*-test and Cramer's V for the $\chi^2$-test/Fisher's exact test. Both give estimates in accordance with Cohen's d that can only be calculated with parametric tests, i.e., small effect = 0.1; moderate effect = 0.3; and large effect = 0.5. An effect size at least approaching the moderate level (0.25 or higher) was considered indicative of a noteworthy group effect.

## 3. Results

There were no differences between pre-BP and pre-SCZ patients on gender, ethnicity, marital status, or graduation from school with the German equivalent of the British A-level (13 years of schooling; required to enter university). However, pre-AD were slightly older than pre-SCZ at baseline (d = 0.09) and pre-AD clearly had better psychosocial functioning at baseline than pre-SCZ (r = 0.36; Table 1).

As displayed in Table 2, similar proportions of pre-SCZ and pre-AD had reported APS and ANS at baseline. However, pre-SCZ had higher positive, negative, and disorganized total scores and a higher mean score on "disorganized communication" (Table 2). These differences approached moderate effect sizes. Moreover, pre-SCZ scored higher than pre-AD on 4 of the 6 negative items ("avolition", "decreased expression of emotion", "decreased ideational richness", and "deterioration in role functioning") and on the general item "impaired tolerance to stress". They did not score higher on the disorganized items (Supplementary Table 1).

When exploring the differences between pre-AD-P ($n = 7$) and pre-AD-noP ($n = 16$; Table 2), ANS were reported at baseline by an almost equal percentage of patients in both groups. The percentage of patients reporting APS at baseline clearly differed between both groups however. Thereby the 8 pre-AD-noP with APS mainly met the APS threshold by "unusual thought content" (5 of 8) and only rarely by any one of the other 4 positive items (1–2 of 8). Near moderate to strong effect sizes were detected on the majority of the SIPS items and scores, except for the total general score and 2 positive items, "grandiose ideas" and "disorganized communication". Thereby, as expected, pre-AD-P generally showed a more severe psychopathology (Table 2) but, interestingly,