Evidence from clinical patient populations indicates that affective dysregulation is strongly associated with reality distortion, suggesting that a process of misassignment of emotional salience may underlie this connection. To examine this in more detail without clinical confounds, affective regulation-reality distortion relationships, and their clinical relevance, were examined in a German prospective cohort community study. A cohort of 2524 adolescents and young adults aged 14–24 years at baseline was examined by experienced psychologists. Presence of psychotic experiences and (hypo)manic and depressive symptoms was assessed at 2 time points (3.5 and up to 10 years after baseline) using the Munich-Composite International Diagnostic Interview. Associations were tested between level of affective dysregulation on the one hand and incidence of psychotic experiences, persistence of these experiences, and psychotic Impairment on the other. Most psychotic experiences occurred in a context of affective dysregulation, and bidirectional dose-response was apparent with greater level of both affective dysregulation and psychotic experiences. Persistence of psychotic experiences was progressively more likely with greater level of (hypo)manic symptoms (odds ratio [OR] trend 5 1.51, P < .001) and depressive symptoms (OR trend 5 1.15, P 5 .012). Similarly, psychotic experiences of clinical relevance were progressively more likely to occur with greater level of affective dysregulation (depressive symptoms: OR trend 5 1.28, P 5 .002; (hypo)manic symptoms: OR trend 5 1.37, P 5 .036). Correlated genetic liabilities underlying affective and nonaffective psychotic syndromes may be expressed as correlated dimensions in the general population. Also, affective dysregulation may contribute causally to the persistence and clinical relevance of reality distortion, possibly by facilitating a mechanism of aberrant salience attribution.

Key words: epidemiology, adolescent, psychosis, affective symptoms
Introduction

Evidence from multiple domains indicates that affective dysregulation is strongly associated with reality distortion. Genetic epidemiological studies have demonstrated that the liabilities for bipolar disorder and schizophrenia are correlated. Psychopathological studies have demonstrated that psychotic experiences are reported within the context of a range of affective clinical disorders, and conversely, high rates of affective symptoms have been demonstrated in patients diagnosed with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), nonaffective psychotic disorders, and schizotypy. Specific aspects of delusional content and severity of psychotic experiences are associated with dysfunctional emotional processes. Although most of the work in this area is cross-sectional and conducted in clinical samples, making it difficult to disentangle the direction of effects between affective and cognitive processes, and to distinguish between illness cause and illness consequence, the strong and consistent associations between affective states and reality distortion may imply causality.

Experimental work by Holt and colleagues indicates that patients with a diagnosis of schizophrenia who had delusions were more likely to assign (negative) affective meanings to neutral stimuli compared with those without delusional ideation. The magnitude of this response bias correlated with the severity of delusions. The findings were interpreted as consistent with an inappropriate activation of a stimulus-independent internal ‚salience detector,‘ leading to misassignment of emotional salience to neutral or ambiguous stimuli, and ultimately to the formation of delusions. Thus, affective dysregulation may result in maladaptive appraisal patterns of events, triggering a search for an explanation of their meaning that in turn increases the risk for positive psychotic experiences in vulnerable individuals. Dysregulation in dopamine transmission, facilitating stimulus-independent release of dopamine, causing aberrant assignment of salience and motivational significance to external objects (leading to delusions) and internal representations of percepts and memories (leading to hallucinations) may represent the underlying neurobiological vulnerability mediating the process of reality distortion.

Research on associations between variable clinical characteristics such as affective symptoms and psychotic experiences in clinical samples cannot examine to what degree such associations may arise as a result of the illness itself, and how interacting affective and cognitive processes, from a perspective of risk, may contribute to the onset of need for care and patient status. Finally, to the degree that the affective and cognitive processes in patients with psychotic disorder are universal, that is, are quantitative variations of normal human mentation, more fundamental knowledge is needed on their association in the general population, as otherwise a correct interpretation of their role in pathological states such as psychotic disorder is not possible.

It has long been recognized that schizophrenia-related pathology is also expressed, at attenuated levels, in individuals with „schizotypal“ or „schizoid“ personality traits. Systematic review of general population surveys indicates that the experiences associated with schizophrenia and related categories, such as paranoid delusional thinking and auditory hallucinations, are observed, in an attenuated form, in 5%–8% of healthy people. These attenuated expressions may be conceived as the behavioral expression of the underlying distributed liability for schizophrenia and related disorders, just as higher levels of blood pressure express higher liability for cardiovascular disease in a dose-response fashion. This interpretation is validated by longitudinal research showing a link between psychotic
experiences in the general population and later outcomes of psychotic disorder. Since the seminal study by Chapman and colleagues, there is replicatory evidence from 2 birth cohorts and 3 representative general population cohorts that low-grade psychotic experiences such as delusional thinking and mild hallucinatory experiences may precede the diagnosis of psychotic disorder, including clinical diagnosis of schizophrenia requiring hospital admission by many years. It has been shown that particularly persistence of subclinical psychotic experiences over time is associated with increased risk of later transition to clinically relevant psychosis. Additional evidence is provided by a body of work on help-seeking individuals with low-grade psychotic experiences who, when followed over time, display high conversion rates to clinical psychotic disorder.

Therefore, epidemiological research in the general population can be useful in complementing clinical research on the link between affective dysregulation, emotional salience misattribution, and psychosis, particularly when a longitudinal perspective can be added in order to clarify the direction of effects and to study the relationship with onset of impairment. Earlier general population surveys in Greece and the Netherlands have shown a high degree of overlap between psychotic experiences and affective symptoms below the threshold for clinical disorder. For the current study, it was hypothesized that (1) level of affective dysregulation, in the form of depression or (hypo) mania symptoms (regardless of the presence of formal mood disorder) in the general population, would be strongly and linearly associated with experience of reality distortion, expressed as psychotic experiences, (2) presence of affective dysregulation would be associated with persistence of reality distortion over time, and (3) affective dysregulation would be associated with Psychotic Impairment in the context of reality distortion.

Methods

Study Design and Population

The Early Developmental Stages of Psychopathology (EDSP) study is a prospective-longitudinal cohort community study which collected data on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders. Following ethics committee approval, a representative population sample was randomly drawn from the 1994 German government population registers. The sample consisted of adolescents and young adults living in the Munich area aged 14–24 years at baseline. Because the primary goal of the study was to examine the incidence and developmental risk factors for psychopathology, stratification of the sample was performed by sampling 14- and 15-year-olds, presumed to have the highest incidence density, at twice the rate of 16- to 21-year olds, and by sampling 22- to 24-year-olds at half this rate. The 4809 sampled individuals were approached through letter and phone. Of these, 4263 were located and determined to be eligible for the study. Most interviews took place at the participant’s home. The study consisted of a baseline survey (T0, n = 3021) and 3 follow-up investigations (T1, T2, and T3), covering a time period of approximately 1.6 years (T0–T1, SD = 0.2), 3.5 years (T0–T2, SD = 0.3), and 8.6 years (T0–T3, range 7.4–10.6 years, SD = 0.7), respectively. Written informed consent was obtained from all participants. The study design and sample have been described in detail in previous reports.

Instruments

Interviews were conducted using the Computer-Assisted Personal Interview (CAPI) version of the Munich- Composite International Diagnostic Interview (DIA-X/M-CIDI), an updated version of the World Health Organization’s CIDI version 1.2. The DIA-X/M-CIDI is a
comprehensive, fully standardized diagnostic interview and assesses symptoms, syndromes, and diagnoses of various mental disorders in accordance with the definitions and criteria of DSM-IV, along with information about onset, duration, severity, and psychosocial impairment. The CIDI is divided into 16 sections: a sociodemographic section, 12 sections consisting of 288 symptom questions regarding groups of mental disorders and 3 final sections containing concluding questions, interviewer observations, and interviewer ratings. High validity as well as high interrater and test-retest reliability of the CIDI have been established. In order to ensure reliability of the assessments, fully trained and experienced clinical psychologists who were allowed to probe with clinical follow-up questions conducted the interviews. At baseline, the lifetime version of the DIA-X/M-CIDI was used; for the follow-up interviews, the DIA-X/M-CIDI interval version was used, covering the respective time periods between interviews. As data on the DIA-X/M-CIDI G-section concerning psychosis and its clinical relevance were only collected at T2 (lifetime version, assessing lifetime cumulative incidence up to T2) and T3 (interval version, assessing onset of new, incident, symptoms or interval rate of any symptom between T2 and T3), the current analyses are limited to T2 and T3. The response rate was 84% at T2 (n = 2548) and 73% at T3 (n = 2210), covering an interval period of 4.9 years on average (SD = 0.6).

Assessment of Reality Distortion

Information from the CIDI psychosis section and the clinical interview rating section with its embedded Brief Psychiatric Rating Scale were used to derive measures of the psychosis dimensions. In order to calculate measures of frequency of psychopathological experiences, such as lifetime cumulative incidence and interval incidence rates, as well as persistence estimates, discrete variables indicating their presence or absence across interview waves were, per definition, necessary.

Reality distortion, expressed as psychotic experiences, was the focus of the current analyses. All expressions of psychotic experiences, regardless of the presence of a formal psychotic disorder, were included. Psychotic experiences were assessed at T2 and T3 using the DIA-X/M-CIDI core psychosis section on delusions (14 items), hallucinations (5 items), and passivity (1 item). Specifically, items used were G1, G2a, G3–G5, G7–G13, G13b, G14, G17, G18, G20, G20c, G21, and G22a. These items concern classic psychotic symptoms including but not limited to persecution, thought interference, and passivity phenomena. Participants were first asked to read a list of all the psychotic experiences and then asked whether they ever experienced such symptoms by the psychologist (list and phrasing available upon request). All these psychosis items can be rated in 2 ways: 1 (absent) and 5 (present), without intermediate levels. The presence of positive psychotic experiences was defined as any rating of „5“ on any of the 20 DIA-X/M-CIDI core psychosis items. In order to examine dose-response as a function of level of psychotic experiences, an additional variable was constructed reflecting the presence of 0, 1, 2, or 3 or more psychotic experiences (hereafter: Psychosis Load).

Assessment of Psychotic Impairment

In order to assess functional impact of psychotic experiences, secondary dysfunction and help-seeking behavior were examined in individuals with evidence of DIA-X/M-CIDI psychotic experiences at T2 and T3; the following procedures were followed as described in an earlier report. First, 2 DIA-X/M-CIDI psychosis section items for help-seeking were used: G16 (delusions) and G23 (hallucinations). These items were phrased as follows: „Did you tell a doctor about„(insert the psychosis section beliefs/experiences previously
acknowledged by the participant along with a visual representation from the response booklet) you have had?“ These items were rated in a dichotomous manner (0 = no, 1 = yes). In addition, participants were shown a list on which several types of outpatient or inpatient institutions for mental health problems were mentioned, ranging from general practitioner or school psychologist to psychiatric sheltered housing, and asked whether they had ever sought help at any of these institutions because of psychotic symptoms as elicited in the DIA-X/M-CIDI G-section. This item was rated in a dichotomous manner (0 = no, 1 = yes). Using these 3 help-seeking items, a dichotomous variable „Help-seeking“ was constructed, indicating whether help-seeking behavior had been present (1) or absent (0).

Second, the level of dysfunction related to psychotic experiences was assessed using the DIA-X/M-CIDI items G28, G29, G29a, and G36. The dysfunction score assessed the effect of the psychotic experiences on: (1) feeling upset, unable to work, go places, or enjoy oneself, at the time of having these experiences (item G28); (2) being less able to work since these experiences began (item G29); (3) being less able to make friends or enjoy social relationships since these experiences began (item G29a); and (iv) how much their life and everyday activities were impaired when these experiences were at their worst (item G36). These 4 psychosis section items were rated in a dichotomous manner (0 = no, 1 = yes). A dichotomous variable „Dysfunction“ was constructed, representing a positive answer on any of the 4 questions (value label 1) vs negative answers on all 4 questions (value label 0).

Based on these 2 assessments, a combined outcome was created (hereafter „Psychotic Impairment“). Psychotic Impairment was absent and scored as „0“ for subjects scoring „0“ on both help-seeking behavior and dysfunction. Subjects scoring „1“ on either or both help-seeking behavior and dysfunction scored „1“ on Psychotic Impairment.

Validation of this variable using third variables was presented previously, using 2 variables: Caseness and Antipsychotic Treatment. Briefly, The X16 DIA-X/MCIDI item rated the interviewer’s opinion regarding clinical evidence of psychological ill-health in 4 levels: essentially not noticeable (0), not very noticeable (1), clearly ill (2), and very ill (3). The dichotomous variable ‘Caseness’ indicated individuals with a noticeable level of psychiatric caseness (any score above „1“). As part of the CIDI treatment module, participants were shown a list of different types of medication, rating their use because of any psychopathological or psychosomatic problem. The acknowledgement of any antipsychotic medication (Q1EA4) reported at T2 and T3 was used to derive treatment („Antipsychotic Treatment“: 0 = no, 1 = yes). Validation analyses revealed that Psychotic Impairment was strongly associated with both the Caseness (odds ratio [OR] = 10.3, 95% confidence interval [95% CI] = 7.0–15.2) and the Antipsychotic Treatment (OR = 15.3, 95% CI = 6.1–38.4) variable.

Assessment of Affective Dysregulation

Affective dysregulation was assessed at T2 and T3 using the 28 symptom items (DSM-IV and International Classification of Diseases, Tenth Revision [ICD-10]) of the DIA-X/M-CIDI depression and dysthymia section (items regarding feeling depressed, loss of interest, loss of energy, hopelessness, decreased concentration, loss of appetite, weight loss, sleep disturbances, feelings of worthlessness or guilt, decreased self-esteem, and suicidal ideation/attemp) and the 11 symptom items of the DIAX/M-CIDI mania section (items regarding increase in goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, increased self-esteem or grandiosity, decreased need for sleep, and distractibility). Symptom items were rated either yes or no.
Depression symptoms were only rated if present for at least 2 weeks; (hypo)mania symptoms if present for at least 4 successive days. In case the participant endorsed the presence of a particular symptom, additional probes ascertained whether the symptom was the direct result of alcohol or drug use or of physical diseases or conditions. If this were the case, the CIDI codes for substance use or somatically induced symptoms were used, and the item was not counted toward the diagnosis of a primary mood disorder. Furthermore, symptoms were only assessed and rated if at least one of the DIA-X/M-CIDI core depressive (depressed mood or loss of interest/pleasure) or core (hypo)mania symptoms (unusual happiness or excitement or unusual irritability) was present. Only participants having core (hypo)mania symptoms that were either noticed by others or because of which participants experienced problems were included.

**Binary and Continuous Affective Variables**

Both binary and continuous affective variables were constructed as described previously:

i) „Binary (hypo)mania“ and „binary depression“: An a priori binary (hypo)mania variable was defined as at least 2 DIA-X/M-CIDI mania symptoms and a binary depression variable as at least 3 DIA-X/M-CIDI depression symptoms.

ii) In addition, guided by previous work, a continuous „(Hypo)mania Score“ and a continuous „Depression Score“ variable were constructed. These variables represented 2 continuous sum scores of symptom ratings: a sum score of (hypo)mania symptoms with a minimum of 0, and a maximum score of 11 endorsements (hereafter: „(Hypo)mania Score“), and a sum score of depression symptoms with a minimum of 0, and a maximum score of 28 endorsements (hereafter: „Depression Score“).

iii) Subsequent to (ii), we created, for both symptom groups, progressively stricter and overlapping subcategories of these sum scores, indicating the degree of symptom loading. For depression, 6 categories were created of no symptoms (0), at least 1 symptom (1), at least 3 symptoms (2), at least 5 symptoms (3), at least 7 symptoms (4), and at least 9 symptoms (5). For (hypo)mania, the categories were similar except that the highest category was at least 5 symptoms due to the very small number of subjects with 6 or more symptoms.

**Statistical Analysis**

Analyses were conducted in STATA, version 10. Associations were expressed as OR and 95% CIs derived from logistic regression.

Associations Between Affective Dysregulation and Psychotic Experiences. Cumulative incidence measures of affective dysregulation and psychotic experiences up until T2 were tested for association in order to establish their lifetime comorbidity (risk set n = 2524). Similarly, interval incidence of psychotic experiences at T3 (i.e., individuals with psychotic experiences at T3 free from psychotic experiences at T2) were modeled as a function of measures of level of affective dysregulation at T3 (risk set n = 1564). This latter analysis provided a temporally more precise test of the hypothesis that affective dysregulation accompanies the onset of psychotic experiences. Finally, T2 and T3 associations between individual psychotic experiences on the one hand and the level of depressive and (hypo)mania symptoms on the other were tested in order to gain insight in possible patterns of association between specific psychotic experiences and affective dysregulation.
Psychosis Persistence. In order to assess the association between level of affective dysregulation and persistence of psychotic experiences over the period T2–T3, associations between T3 level of affective dysregulation and T3 psychotic experiences were assessed in individuals with evidence for psychotic experiences at T2 (risk set $n = 464$).

Psychotic Impairment. In order to assess the relationship between level of affective dysregulation and incident Psychotic Impairment, associations between T3 Psychotic Impairment and T3 level of affective dysregulation were assessed in individuals with evidence of psychotic experiences at T3 but free from Psychotic Impairment at T2 (risk set $n = 191$).

Results

At T2, over half (51%) of the sample was male and the mean age was 21.7 years (SD 3.4). At T2, 574 (23%) of all subjects presented with one or more lifetime psychotic experiences, with a stronger representation of delusions (21%) compared with hallucinations (5%). At T3, the rates were lower, representing only the occurrence of psychotic experiences over the interval from T2 to T3 (table 1). At T2, 978 subjects (32%) had experienced 2 or more (hypo)mania or 3 or more depression symptom; at T3, this was the case for 925 subjects (31%). Within the subgroup of subjects with 2 or more (hypo)mania or 3 or more depression symptoms at T2 ($n = 978$), 57% did not report similarly defined (hypo)mania or depression symptoms at T3. Conversely, within the subgroup of subjects that did not experience 2 more (hypo)mania or 3 or more depression symptoms at T2, 25% did present similarly defined (hypo)mania or depression symptoms at T3. The lifetime cumulative incidence up until T2 and the T2–T3 interval rates, assessed at T3, of hallucinations, delusions, (hypo)mania, and depression symptoms are provided in table 1.

Affective Dysregulation and Reality Distortion Co-occurrence

Of the 574 subjects with psychotic experiences, 35% also presented with at least 2 (hypo)mania symptoms at T2, compared with 15% of subjects without lifetime psychotic experiences at T2. At T3, these figures were 27% and 11%, respectively. Similarly, 43% of the 574 subjects with psychotic experiences presented with at least 3 depression symptoms at T2, compared with 23% of subjects without psychotic experiences. At T3, these figures were 46% and 31%, respectively. At both T2 and T3, the majority of psychotic experiences occurred in the context of affective dysregulation (at least 2 (hypo)mania symptoms or at least 3 depression symptoms; table 2).

Bidirectional Dose-Response Associations Between Affective Symptoms and Reality Distortion

The probability of lifetime psychotic experiences at T2 was progressively higher with greater level of co-occurrent affective dysregulation in a dose-response fashion ((Hypo) mania Score OR linear trend over 4 levels = 1.70, 95% CI: 1.55, 1.87; $P < .001$; Depression Score OR linear trend over 6 levels: OR = 1.31, 95% CI: 1.24, 1.38; $P < .001$; table 3). Incident psychotic experiences at T3 (ie psychotic experiences at T3 in subjects free from psychotic experiences at T2) were similarly associated with (Hypo)mania Score and Depression Score in a dose-response fashion (table 3).
Similarly, the above OR linear trends expressing the association between psychotic experiences and affective dysregulation became progressively greater at higher level of Psychosis Load, both for mania and depression, and both at T2 and at T3 (table 4).

**Psychosis Persistence**

(Hypo)mania Score and Depression Score were associated with persistence of psychotic experiences over the period T2–T3. Thus, within the sample of subjects with psychotic experiences at T2 and interviewed again at T3 (risk set n = 464), the probability of persistence of psychotic experiences was progressively greater with higher (Hypo)mania Score (OR linear trend 4 categories = 1.51; 95% CI: 1.22, 1.88; P < .001) and higher Depression Score (OR linear trend 6 categories = 1.15; 95% CI = 1.03, 1.28; P = .012).

**Psychotic Impairment**

In all, 228 subjects (9%) presented at T2 with Psychotic Impairment. At T3, the number with Psychotic Impairment was 118 (5%). Of these 118, 70 subjects had not presented previously with Psychotic Impairment at T2, representing incident Psychotic Impairment. Affective dysregulation was associated with incident Psychotic Impairment: within the sample of subjects without Psychotic Impairment at T2 and presence of at least one psychotic experience at T3 (risk set n = 191), the probability of Psychotic Impairment at T3 as progressively higher with higher (Hypo)mania Score at T3 (OR linear trend 4 categories = 1.37, 95% CI: 1.02, 1.83; P = .036) and higher Depression Score at T3 (OR linear trend 6 categories = 1.28, 95% CI: 1.10, 1.49; P = .002).

**Associations Between Affective Dysregulation and Specific Psychotic Experiences**

An overview of specific psychotic experiences and associations with binary depression (at least 3 symptoms) and (hypo)mania (at least 2 symptoms) variables is provided in table 5. For both depression and (hypo)mania symptoms, no specific trend or pattern was apparent among the different psychotic experiences.

**Discussion**

Clinical studies in help-seeking samples suggest that early intervention in the prodromal phase of psychotic disorder may be feasible. However, knowledge on the developmental mechanisms underlying the epidemiology of prodromal states in the general population remains very limited. The current study connects reality distortion and affective dysregulation in a general population setting from a perspective of risk and a perspective of understanding links with normal mentation. The results suggest that psychotic experiences in the general population are nonspecifically associated with affective dysregulation, in a bidirectional dose-response fashion. Second, persistence of psychotic experiences and the onset of impairment associated with reality distortion occur more often if there is a context of affective dysregulation.

**Coexpression as a Reflection of Overlapping Genetic Liabilities**

Although the delusions and hallucinations of psychosis can be readily recognized, classifying psychotic states remains a major challenge. Psychosis is not exclusive to schizophrenia and occurs across a range of diagnostic categories of psychotic disorder and even among the category of nonpsychotic mood disorders. The criteria used to distinguish between the
different categories of psychotic disorder are based on duration, dysfunction, associated
substance use, „bizarreness“ of delusions, and presence of depression or (hypo)mania.
However, the resulting diagnostic categories of psychotic disorder show overlap in genetic
liability among themselves. For example Kendler and colleagues40 demonstrated a significant
familial relationship between nonschizophrenic psychotic disorders with both schizophrenia
and schizotypal personality disorder. Family and twin studies similarly demonstrate a degree
of overlap in genetic liability between nonaffective psychotic disorder and bipolar disorder.3–5
Coexpression of (subclinical) affective dysregulation and psychotic experiences in general
cohort studies may, thus, in part reflect overlapping distributed genetic vulnerabilities. The
majority of general cohort studies on transition rates from subclinical symptoms to clinical
syndromes did not examine coexpression of reality distortion and affective dysregulation.
Multiple studies suggest that subclinical psychotic experiences increase the risk for
nonaffective psychotic disorder,19–24 and similarly subthreshold depression and/or
(hypo)mania symptoms have been shown to increase the risk for bipolar disorder.35,36 Overall,
affective dysregulation and reality distortion have been shown to represent the behavioral
expression of risk for more severe psychotic states including schizophrenia and bipolar
disorder in the general population. In light of the accumulating evidence on overlap in genetic
liability,3–5 suggesting a broad underlying vulnerability that expresses across the different
categories, our findings of associations between affective dysregulation and psychotic
experiences in the general population may therefore simply reflect passive clustering of the
behavioral expression of overlapping genetic risks.

Coexpression as a Reflection of Causal Influence

The fact that coexpression of affective dysregulation predicted persistence of reality distortion
and impairment associated with psychotic experiences suggest that, in addition to correlated
 genetic liabilities, a direct impact of affective dysregulation on the onset of psychotic
experiences may be hypothesized. Existent psychological models of symptom formation
suggest that the emotional context, and associated beliefs or appraisals, may induce bias in
 logical reasoning processes and, therefore, provoke reality distortion in healthy individuals.2,15
In the psychological model described by Garety and colleagues,1 the experience of a stressful
 event is thought to potentially give rise to altered preexisting beliefs and ongoing appraisals of
experiences due to a certain emotional change or a cognitive processing bias. These distorted
processes may lead to aberrant experiences that may seem personally significant to the
individual and are likely to trigger a search for an explanation as to their meaning and cause
that is consistent with affect-associated beliefs. Biased appraisal processes may contribute to a
judgment that the experience is in fact externally caused. It is the interpretation that causes the
associated distress and disability, rather than the experience itself. Thus, maladaptive
appraisal patterns, induced by emotional processes, are suggested to increase the risk for
positive symptom formation in vulnerable individuals.1 Our findings provide support for a
cognitive model of symptom formation, by demonstrating involvement of affective processes
in the onset and persistence of reality distortion outside the context of disorder.

Linking Genetic and Cognitive Mechanisms

Evidence on the role of cognitive processes suggests that cognitive biases and appraisals can
help explain onset of psychosis.1 Attempts have been made to integrate cognitive and
neurobiological theories into a single model of psychotic states.1,16,41 Thus, evidence indicates
that genetic risk for psychotic disorder is associated with underlying alterations in the
dopamine system, including increased dopamine synaptic availability,42 increased striatal
dopamine synthesis, and increased dopamine reactivity to stress. Under normal circumstances, it is the context-driven activity of the dopamine system that mediates the experience of novelty and the acquisition of appropriate motivational salience, detecting new rewards in the environment that facilitate learning and goal-directed behavior. Certain cerebral vulnerabilities, occasioned by interplay between genetic and environmental risks, could trigger context-independent or context-inappropriate release of dopamine. A dysregulated dopamine system may cause aberrant assignment of salience and motivational significance to external objects (leading to delusions) and internal representations of percepts and memories (leading to hallucinations). Thus, theory derived from existent psychological models of psychotic symptom formation predicts that affective dysregulation may impact directly on risk for reality distortion. An integrated model would additionally suggest that the risk to develop a clinical disorder is particularly high in those who additionally have a genetic liability for dopaminergic dysregulation, facilitating aberrant salience attribution.

Limitations

Several limitations should be taken into account when interpreting these results. First, the study was epidemiological, and no direct measurements of affective and cognitive processes such as aberrant salience attribution were available, limiting the explanatory power of the findings on these mechanisms. Second, although longitudinal, measurements were too far apart for dynamic models of the onset of impairment as a function of affective dysregulation. Third, assessment of psychotic experiences, while better than lay-interviewer assessed self-reports, will likely contain false-positive answers even when interviewers are clinical psychologists. However, it is unlikely that false-positive assessments would produce spurious associations with affective dysregulation – the opposite, more conservative alternative is more likely. Furthermore, the substantial literature on self-reported psychotic experiences, including those assessed with the DIA-X/MCIDI, indicates substantial predictive and other forms of validity of these phenomena. Fourth, lifetime rates in excess of 22% may seem high, given an estimate of 5%–8% in a recent systematic review. However, in another systematic review we are preparing, it is apparent that rates of psychotic experiences are critically dependent on the number of items assessing different psychotic experiences. Previous work using the CIDI also detected rates close to 20%. Finally, it could be argued that the measure of psychotic Impairment used was broad, resulting in a lifetime rate of 9%, which may be considered very high for psychosis. The high rate is in part inherent to the population-based research paradigm of EDSP, which will always detect many more cases compared with the much lower administrative rates reflecting treatment at the level of services. Furthermore, even the rate of narrowly defined clinical psychotic disorder, when assessed completely, may be as high as 3.5%. In addition, to the degree that our definition of impairment was broad, it can be argued that in this context, sensitivity is more important than specificity, given the fact that the main clinical application of research on extended phenotypes ultimately is situated in the area of early detection.

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Conflict of Interest:
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References

24. Werbeloff N, Dukker M, Dohrenwend B. Self-reported psychotic symptoms in the community are associated with increased risk of later hospitalisation for non-affective psychotic disorders. Schizophr Bull. 2009;35(suppl 1):74.