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Evidence That Onset of Psychosis in the Population Reflects Early Hallucinatory Experiences That Through Environmental Risks and Affective Dysregulation Become Complicated by Delusions

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Objective: **To examine the hypothesis that the "natural" combination of delusions and hallucinations in psychotic disorders in fact represents a selection of early subclinical hallucinatory experiences associated with delusional ideation, resulting in need for care and mental health service use.** ***Methods:*** **In the Early Developmental Stages of Psychopathology study, a prospective, 10-year follow-up of a representative cohort of adolescents and young adults in Munich, Germany ($n = 2524$), clinical psychologists assessed hallucinations and delusions at 2 time points (T2 and T3). Analyses compared differences in psychopathology, familial liability for nonpsychotic disorder, nongenetic risk factors, persistence, and clinical outcome between groups characterized by: (1) absence of positive psychotic symptoms, (2) presence of isolated hallucinations, (3) isolated delusions, and (4) both hallucinations and delusions.** ***Results:*** **Delusions and hallucinations occurred together much more often (T2: 3.1%; T3: 2.0%) than predicted by chance (T2: 1.0%; T3: 0.4%; OR = 11.0; 95% CI: 8.1, 15.1). Content of delusions was contingent on presence of hallucinations but modality of hallucinations was not contingent on presence of delusions. The group with both hallucinations and delusions, compared to groups with either delusions or hallucinations in isolation, displayed the strongest associations with familial affective liability and nongenetic risk factors, as well as with persistence of psychotic symptoms, comorbidity with negative symptoms, affective psychopathology, and clinical need.** ***Conclusions:*** **The early stages of psychosis may involve hallucinatory experiences that, if complicated by delusional ideation under the influence of environmental risks and (liability for) affective dysregulation, give rise to a poor prognosis hallucinatory–delusional syndrome.**

Key words: psychosis/delusions/hallucinations/schizophrenia/prevention/risk

Introduction

The early origins of psychotic illness in the general population remain poorly understood.[1] Informative findings come from a handful of prospective general population studies showing that the onset of psychotic disorder can be seen as the outcome of earlier subthreshold expressions of psychotic signs and symptoms.[2–4] Study results show that the majority of persons with subthreshold expression of psychotic symptoms (prevalence: 5%–10%[5]) never convert to psychotic disorder and that in those who do, the number and severity of subthreshold psychotic symptoms, and their degree of persistence, under the influence of environmental exposures such as childhood trauma, cannabis use and an urban environment,[6,7] are important predictors.[8] Furthermore, not just the presence of psychotic symptoms per se, but the psychopathological and developmental context determines the longer-term outcome, particularly the degree of admixture with affective dysregulation, negative symptoms, and premorbid social dysfunction.[9–11]

One important hypothesis that has remained difficult to examine empirically regards the relationship between perceptual abnormalities and delusional ideation in the early expression of psychosis. Whilst delusions and hallucinations in psychotic disorder are seen as symptoms that naturally pertain to the same "class" of positive symptoms, they in fact refer to very different phenomena and there is very

little research, or empirical evidence, on possible reasons and consequences for their co-occurrence. The observed correlation between delusions and hallucination has only rarely been the topic of empirical research, in terms of going beyond mere correlation to actual investigation of what this correlation may mean, comparing, on the one hand, delusions and hallucinations in isolation vs, on the other, their co-occurrence in relation to etiological and clinical parameters. In clinical samples this would be difficult, given correlations secondary to Berkson's bias or comorbidity bias,[12,13] and the fact that antipsychotic treatments successfully suppress (clustering of) positive psychotic symptoms. At the general population level, however, comparative empirical research is valid and important, as in individuals with subclinical expression of symptoms, the pathway from early expression to clinical needs may critically depend on level of "comorbidity" of symptoms, and its clinical consequences, over time.

Many of the theories that have relevance for the observation of co-occurrence of delusions and hallucinations[14–20] contain elements that, at least in part, are compatible with arguably the oldest and best established theory, that delusions may be seen as "complicating" abnormal perceptual processes[21–23] or, as described more recently, aberrant attribution of salience.[24] This theory has some empirical support[25–28] and is of major clinical relevance, as it implies that clustering of hallucinatory and delusional ideation represents a significant deepening of the psychotic state. There is some support for this hypothesis, given evidence that clustering of hallucinations and delusional ideation is particularly likely in the presence of affective dysregulation,[29] a factor which previous work suggests is essential in the early formation and clinical outcome of psychotic experiences.[9,30–35]

The theory that hallucinatory experiences may present with or without delusional ideation is particularly relevant from the early psychosis perspective, as it suggests that the co-occurrence of delusions and hallucinations in psychotic disorder may not be "natural" but, on the contrary, the result of a dynamic selection with prognostic consequences: of the individuals in the general population who experience anomalous perceptions, those with "comorbid" delusional ideation may be more likely to develop need for care and thus become diagnosable cases when they present to psychiatric services.

The current analysis focused on a general population sample that was followed over time, with repeated assessments, administered by clinical psychologists, of the spectrum of psychotic symptoms, in combination with assessment of dysfunction and help-seeking. The following hypotheses were examined:

1. Hallucinations and delusions cluster together more often than would be expected by chance.
2. Co-occurrence of delusions and hallucinations, compared to either one in isolation, is more strongly associated with parameters predicting transition to clinical outcome, such as more persistence over time, comorbid affective dysregulation, negative symptoms, suicidal ideation, anxiety, and familial psychopathology.
3. Although it is difficult to directly examine the hypothesis relating to the more theoretical issue that the dynamic sequence over time is from hallucinations to secondary delusional ideation, this hypothesis can be examined indirectly by showing that (1) the content of delusions differs as a function of whether or not hallucinations are present whereas (2) modality of hallucinations does not vary as a function of whether or not delusions are present. In other words, confirmation of hypothesis III would yield evidence that delusions "follow" hallucinations but not the other way around.
4. Co-occurrence of delusions and hallucinations, compared with either one in isolation, is more strongly associated with environmental exposures, such as childhood trauma, cannabis use, and an urban environment.

Methods

Sample

Data were from the Early Developmental Stages of Psychopathology (EDSP) Study, which collected data on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders in a random, representative population sample of adolescents and young adults in the general population. The baseline sample was randomly drawn, in 1994, from the respective population registry offices of Munich and its 29 counties to mirror the distribution of individuals expected to be 14–24 years of age at the time of the baseline (T0) interview in 1995. More details on the sampling, representativeness, instruments, procedures, and statistical methods of the EDSP Study sample have previously been presented.[36,37] The EDSP study was approved by the Ethics Committee of the Technical University Dresden.

Study Design

The design of EDSP is longitudinal and prospective, consisting of a baseline (T0) and 3 follow-up surveys, covering a time period of on average 1.6 years (T0–T1, SD = 0.2), 3.5 years (T0–T2, SD = 0.3), and 8.4 years (T0–T3, range = 7.3–10.5 years, SD = 0.7). Because the primary goal was to examine the incidence and developmental risk factors for psychopathology, the younger group (14–15 years), presumed to have the highest incidence density, was sampled at twice the rate of persons aged 16–21 years, and the oldest group (22–24 years) was sampled at half this rate. For the same reason, subjects aged 14–17 years at baseline were examined at the 4 time points, and subjects aged 18–24 years were assessed

only 3 times. Written informed consent was obtained from all subjects.

The G-section of the DIA-X/M-CIDI, which focuses on psychosis, was administered at T2 (lifetime version section G) and T3 (interval version T2–T3 of section G). For the current article and analyses, the T2 sample served as baseline because psychotic symptoms were first assessed at T2. The baseline sample consisted of 3021 individuals aged 14–24 years; at T2, 2548 participants were reinterviewed (response rate = 84%) and 2210 (73%) at T3.

Instruments

The Self-report Symptom Checklist-90R. At all time points, participants completed the previously validated self-report symptom checklist-90R (SCL-90R), the time frame of which is the past 2 weeks, oriented to screen for a broad range of psychological problems and psychopathology.[38] It contains 90 items, scored on a 5-point severity scale, measuring 9 primary symptom dimensions named "somatization," "obsessive-compulsive," "interpersonal sensitivity," "depression," "anxiety," "hostility," "phobic anxiety," "paranoid ideation," and "psychoticism."

The Munich-Composite International Diagnostic Interview. Participants were assessed using the computerized version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI),[39,40] an updated version of the World Health Organization's CIDI version 1.2.[41] 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 the International Classification of Diseases, Tenth Revision (ICD-10) and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), along with information about onset, duration, severity of symptoms, and psychosocial impairment as well as interviewer observations.

As the assessment of psychosis with the CIDI by lay interviewers is not considered reliable,[40,42] trained clinical interviewers at the level of clinical psychologist, who were allowed to probe with follow-up clinical questions, conducted the interviews in the respondents' homes.

At baseline, the DIA-X/M-CIDI lifetime version was used. At each of the follow-up assessments, interviewers administered the interval version, covering the period from the last interview until the next.

Psychopathology. "Hallucinations and delusions" were assessed at T2 and T3 with the G-section of the DIA-X/M-CIDI. G-section delusions were: being spied on (G1), being followed (G2), being tested (G3), conspiracy (G4), being loved by a stranger (G5), can read thoughts (G7), can hear thoughts of other people (G8), thoughts being heard by others (G9), controlled by force (G10), being given thoughts (G11), thoughts being taken (G12), messages specially directed at the person (G13), song or book directed specially at the person (G13b), influenced by strange force (G14), and forced to move (G22a). G-section hallucinations were: seeing things which others could not see (G17), hearing things which others could not hear, like voices or noises (G18), smelling things which others did not smell (G20), having a strange taste in the mouth without reasonable explanation (G20c), and feeling things or sensations on one's body without external stimulus (G21a). Each variable was coded 1 if the item was present and 0 if the item was absent. At both T2 and T3, a variable (hereafter: group) denoting the different combinations between delusions and hallucinations was constructed as follows: "no psychotic symptoms" (value "0"; all delusions = 0 and all hallucinations = 0), "isolated delusions" (value "1"; any delusion = 1 and all hallucinations = 0), "isolated hallucinations" (value "2"; all delusions = 0 and any hallucination = 1), hallucinations and delusions (value "3"; any delusion = 1 and any hallucination = 1).

At T2 and T3, 2 items concerning negative and disorganized symptoms from the DIA-X/M-CIDI interview ratings X-section were used: (1) indifference (X11) and (2) thought incoherence and/or illogicality (X12). In addition, at T2, not only items X11 and X12 were assessed but also 5 items of the DIA-X/M-CIDI interview observational P-section were available: flat affect (item P03), slow speech (item P05), reduced movement (item P06), reduced speech (item P07), and lack of goal-directed behavior (item P08). All items were rated dichotomously as absent or present. Conform previous analyses in this sample,[43] a dichotomous variable "negative symptoms" was created, a value of 0 indicating ratings of absent on all 7 items of the X- and P-sections at T2 and the 2 X11 and X12 items at T3, a value 1 indicating a rating of present on any of the 7 items at T2 and any of the 2 items at T3. T2 and T3 measures of negative symptoms were described and validated in a previous publication.[10]

Depressive and Manic Symptoms. Depressive and manic symptoms were assessed at T2 and T3 using the 28 symptom items of the DIA-X/M-CIDI depression and dysthymia section and the 11 symptom items of the DIAX/M-CIDI mania section that follow the DSM-IV and ICD-10 criteria. As described previously,[9] a continuous "(hypo)mania score" was constructed consisting of the sum score of manic symptoms with a theoretical range of 0–11 symptoms, recategorized to 4 categories of increasing numbers of manic symptoms. Similarly, a continuous sum score of depression symptoms was constructed with a theoretical range of 0–28 symptoms (hereafter: "depression score"), recategorized to 6 categories of increasing numbers of depressive symptoms.[9]

Substance Abuse or Dependence. T2 and T3 alcohol dependence or abuse was assessed dichotomously (absence = 0, presence = 1) using section I of the DIA-X/M-CIDI, which follows the criteria from the DSM-IV. Similarly, at T2 and T3, a dichotomous composite variable indicating any use of cannabis, amphetamine, cocaine, ecstasy, angel dust, opiates, glue, or other drug of abuse in excess of more than 5 times (for each drug separately) was constructed, based on questions regarding drug use from the DIA-X/M-CIDI L-section at T2 and T3, respectively. The rationale for using a cutoff point of "more than 5 times drug use" is described in more detail elsewhere.[44]

Anxiety. The variable "any anxiety disorder" was derived from the DIA-X/M-CIDI D-section, which explores the presence of Panic Disorder with or without agoraphobia, Agoraphobia without a history of panic disorder, Social phobia, Specific phobia, Anxiety disorder NOS, Generalized anxiety disorder, and Obsessive–compulsive disorder. A T2 and T3 dichotomous variable "any anxiety disorder" was constructed indicating the presence of any anxiety disorder at these time points.

Assessment of Persistence of Psychotic and Negative symptoms. Conform previous research in this sample, the SCL-90R psychoticism and paranoid ideation subscales were combined into one Psychosis scale (hereafter "SCL-psychosis scale") by summing their scores.[44] The correlation between this SCL-psychosis scale and the variable expressing the number of M-CIDI psychotic symptoms at T3 (when the interval assessment of the M-CIDI was closest to the time window of 2 weeks of the SCL-90R) was 0.33. For the SCL-90R anxiety scale, the correlation was −0.01, suggesting convergent and discriminant validity of the SCL-psychosis scale. As described previously,[8] a discrete variable for longitudinal persistence of psychotic symptoms was constructed for each participant on the basis of the T0, T2, and T3 measures of the SCL-psychosis subscale by (1) dichotomizing the SCL-psychosis scales around the 90% percentile at each time point and (2) making a score of the number of times individuals had scores in the highest 10% at T0, T2, and T3. Thus, a variable for the 10-year persistence of psychotic symptoms across T0, T2, and T3 was rated 0 (never), 1 (once), or 2 (twice) or 3 (thrice), hereafter "10-year psychosis persistence," which was assessed independently of the measures of T2 and T3 psychotic symptoms described above.

Persistence of Negative Symptoms. Similarly, as described in more detail previously,[43] a variable indicating the 10-year persistence of negative symptoms was constructed based on presence of any negative symptom rated at T0 (assessed in the same fashion as at T3 using the X11 and X12 items, see above), T2 and T3, rated 0 (never), 1 (once), or 2 (twice) or 3 (thrice), hereafter "10-year negative symptom persistence."

Assessment of Clinical Relevance of Positive Psychotic Symptoms. Help-seeking As described previously,[8] help-seeking secondary to psychotic symptoms at T2 and T3 was assessed using 3 DIA-X/M-CIDI items. Two psychosis section items were used: G16 (delusions) and G23 (hallucinations), which were phrased as follows: "Did you tell a doctor about … (the psychosis-section hallucinatory/delusional item previously endorsed by the participant along with a visual representation from the response booklet) you have had?" A third item from the concluding section was added (Q1DG); participants were shown a list of several types of outpatient or inpatient institutions for mental health problems and asked whether they had ever sought help at any of those institutions because of psychotic symptoms from the DIA-X/M-CIDI G section. Using these 3 help-seeking behavior items, a dichotomous variable "help-seeking" was constructed, indicating a positive answer on any of the 3 questions (1) vs negative answers on all 3 questions (0).

Dysfunction As described previously,[8] dysfunction due to psychotic symptoms was assessed using the following DIA-X/M-CIDI G-section items: (G28) feeling upset, unable to work, go places, enjoy oneself at the time of these experiences; (G29) being less able to work since the onset of the experiences; (G29a) being less able to make friends or enjoy social relationship since the onset of these experiences; (G36) how much daily life and everyday activities were impaired when the experiences were at their worst. The dichotomous variable "dysfunction" was rated 1 for any positive endorsement and 0 for a negative rating on all 4 items.

Thinking about Death Conform previous work in this sample,[46] the dichotomous variable "thinking about death" was used as a measure for suicidal ideation. This was assessed at T2 and T3 with the question "Did you think a lot about death in general, your own death or that of other persons?" (DIA-X/M-CIDI item E37).

Caseness The X16 DIA-X/M-CIDI item (assessed at T2–T3) was used to assess "caseness." This item rates the interviewer's opinion regarding clinical evidence of psychological ill health and consists of 4 levels: essentially not noticeable (0), not very noticeable (1), clearly ill (2), and very ill (3). The dichotomous variable "caseness" was defined as any score above 1.

Nongenetic Risk Factors. The variable "trauma at T0" was constructed with the N1-list from the DIA-X/M-CIDI, as described previously.[46]Trauma at T0 was coded 0 (absence of trauma at T0) or 1 (endorsement on any trauma item at T0). Cannabis use was measured with list L1 of the DIA-X/M-CIDI L-section in which

participants had to indicate which substances they used and how often. A dichotomous variable "use of cannabis for 5 times or more at T0" was created and rated as "yes" (value label: 1) or "no" (value label: 0). The last environmental risk factor was "urbanicity T0" (based on information of the German registration office: living in Munich = 1/living rural = 0; the population density of the Munich area is 4601 persons per square mile, that of surrounding areas is 553 persons per square mile).

Assessment of Family History. Given strong associations between psychotic disorder and nonpsychotic disorder in relatives,[47] nonpsychotic parental mental illness variables were calculated on the basis of M-CIDI interviews with the parents at T1 that were only available for the youngest group aged 14–17 years at baseline. Family history variables thus were only created for the younger group. The following disorders, rated absent or present, were derived from the M-CIDI interview: "parental substance abuse and dependence," "parental alcohol abuse and dependence," "parental substance and alcohol misuse." "parental manic symptoms" and "parental depressive symptoms" were assessed at T1 via, respectively, the F-section and the E-section of the M-CIDI. The total number of endorsed items was recoded into a continuous sum score as described above for the variables "depressive score" and "(hypo)mania score."

Analysis

All analyses were carried out using STATA version 11.0.[48] Given the fact that cumulative incidence rates of psychotic symptoms were 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.[43] In order to correct for the clustering of multiple observations within subjects, cluster–robust SEs were computed, using the CLUSTER option in the MLOGIT module in STATA. All analyses were additionally adjusted for age and sex.

It was tested whether the type of delusion discriminated between individuals with only delusions and individuals with both delusions and hallucinations (ie, are delusions contingent on hallucinations) and, conversely, whether the type of hallucination discriminated between individuals with only hallucinations and individuals with both delusions and hallucinations (ie, are hallucinations contingent on delusions).

Multinomial logistic regression of the variable "group" was carried out, estimating associations, expressed as ORs and 95% CI in relation to the following groups of independent variables: (1) outcome: help-seeking, dysfunction, suicidal ideation, caseness, and persistence of positive and negative symptoms; (2) comorbid psychopathology: negative symptoms, depressive symptoms, manic symptoms, any anxiety disorder, any drug use, alcohol abuse/dependence; (3) parental history of nonpsychotic illness: alcohol/substance misuse, depressive symptoms, manic symptoms; and (4) risk factors: trauma, cannabis use, and urbanicity. ORs were compared by Wald test.

Risk Set. Information on the G-section of the DIA-X/M-CIDI was available for 2524 participants at T2 (lifetime version) and for 2210 at T3 (interval T2–T3 version). In the long format, the risk set consisted of 4734 observations, except for the analyses on family history (1787 observations, youngest subgroup only) and the analysis on negative symptoms (4063 observations) due to missing data on the 10-year negative symptom persistence variable.

Table 1. Demographic Characteristics of the Sample at T2 and T3

	T2 (n = 2548)	T3 (n = 2210)[a]
Gender % (n)		
Male	51% (1297)	51% (1135)
Female	49% (1251)	49% (1075)
Mean age (min, max)	21.8 (17, 28)	26.6 (21, 34)
Rural % (n)[b]		
Munchen	70% (1796)	70% (1558)
Rural	30% (752)	30% (652)
Education % (n)[b]		
Low	13% (323)	12% (271)
Medium	30% (769)	29% (647)
High	57% (1456)	58% (1292)
Social economic status % (n)[b]		
Lower	6% (163)	6% (132)
Middle	59% (1492)	56% (1229)
Upper	33% (844)	33% (740)
Other	2% (49)	2% (39)

Note: Level of education: low (mandatory basic school or learning a profession), medium (high school), and high (high school preparing for university, and university level). Participants were asked what education they were attending or what was the highest attended education (demographic section, item A3 of the DIA-X/M-CIDI). Social status: lower (lower class, lower middle class), middle (middle class), upper (higher middle class, upper class), other (none of the above and missing values). Participants were asked to choose from different options in which class they believed to be in (demographic section, item A16 of the DIA-X/M-CIDI). Residence: urban (city of Munich) or rural (surrounding areas of Munich), obtained through German registration office. The population density of the Munich surroundings areas was 553 persons per square mile and that of the city 4601 persons per square mile.
[a]Numbers may not add up to 100% due to rounding.
[b]As assessed at T0.

Results

Subject Characteristics

The sample distribution of demographic variables for T2 and T3 is displayed in table 1.

Table 2. Rates of Delusions and Hallucinations and Observed and Expected Co-occurrence

	Any Hallucination	Isolated Hallucination	Any Delusion	Isolated Delusion	Hallucinations and Delusions Expected[a]	Hallucinations and Delusions Observed
T2 interview (n = 2524)	117 (4.6)	39 (1.6)	529 (21.0)	451 (17.9)	25 (1.0)	78 (3.1)
T3 interview (n = 2210)	69 (3.1)	26 (1.2)	248 (11.2)	205 (9.3)	8 (0.4)	43 (2.0)

[a]Represents the product of the rates of any hallucination (column 2) and any delusion (column 4).

Pattern of Co-occurrence Hallucinations and Delusions

Delusions and hallucinations occurred together much more often (T2: 3.1%; T3: 2.0%) than predicted by chance (T2: 1.0%; T3: 0.4%) (table 2). The OR for association was 11.0 (95% CI: 8.1, 15.1). In addition, delusional content differed as a function of the copresence of hallucinations (table 3): G-section items most likely to distinguish individuals with only delusions from individuals with both hallucinations and delusions were thoughts being heard by others (OR = 4.0, 95% CI: 2.1, 7.3), thoughts being taken (OR = 8.7, 95% CI: 2.3, 33.6), and messages directed at the person (OR = 6.3, 95% CI: 2.9, 14.0). Conversely, however, type of hallucination did not differ as a function of presence of delusions (table 4).

Clinical Relevance, Comorbidity, and Persistence

The pattern of results was that all groups (hallucination and delusions, hallucinations only, delusions only) differed from the reference group without psychotic symptoms on all variables. However, the group with both hallucinations and delusions, compared with the other 3 groups, displayed stronger associations for each variable reflecting clinical relevance (table 5). The highest risk was for the variable help-seeking: 35.5% of individuals with delusions and hallucinations had sought help, compared with 7.7% in the group with only hallucinations, 8.7% in the group with only delusions, and 0.1% in the reference group.

Similarly, individuals with both delusions and hallucinations consistently had the highest rates of comorbidity, although not always at conventional statistical level (table 6). The greatest observed difference was for anxiety disorder: the rate was 45.5% in those with delusions and hallucinations, compared to 26.2% and 21.7% in those with, respectively, only hallucinations and only delusions and 14.2% in the reference group. Similarly, rates of negative symptoms were, respectively, 21.5%, 15.4%, 16.0%, and 11.7%.

Nearly 25% in the group with delusions and hallucinations had persistence of positive psychotic experiences over 2 or 3 measurements, significantly higher than all

Table 3. Prevalence of Specific Delusions in Groups With (1) Any Delusion but No Hallucinations (2) Combination of Any Delusion and Any Hallucination

	% With Specific Delusion in Group With Any Delusion but No Hallucination, (n, %)		% With Specific Delusion in Group With Combination of Any Hallucination With Any Delusion, (n, %)		
Psychotic Symptom	T2 (n = 451)	T3 (n = 205)	T2 (n = 78)	T3 (n = 43)	T2–T3,[a] OR (95% CI)
Being spied on	155 (34.4)	68 (33.2)	31 (39.7)	15 (34.9)	1.2 (0.8, 1.8)
Being followed	86 (19.1)	28 (13.7)	21 (26.9)	12 (27.9)	1.7 (1.1, 2.7)***
Being tested	102 (22.6)	64 (31.2)	23 (29.5)	14 (32.6)	1.4 (0.9, 2.2)
Conspiracy	114 (25.3)	45 (22.0)	33 (42.3)	20 (46.5)	2.4 (1.7, 3.7)*
Loved by stranger	57 (12.6)	24 (11.7)	15 (19.2)	9 (20.9)	1.8 (1.1, 3.1)***
Can read thoughts	69 (15.3)	20 (9.8)	20 (25.6)	10 (23.3)	2.1 (1.3, 3.3)**
Can hear thoughts	41 (9.1)	16 (7.8)	14 (18.0)	7 (16.3)	2.2 (1.3, 3.8)**
Thoughts being heard	21 (4.7)	9 (4.4)	10 (12.8)	9 (20.9)	4.0 (2.1, 7.3)*
Controlled by force	15 (3.3)	6 (2.9)	6 (7.7)	3 (7.0)	2.4 (1.0, 5.8)***
Being given thoughts	10 (2.2)	1 (0.5)	2 (2.6)	1 (2.3)	1.5 (0.4, 5.5)
Thoughts being taken	3 (0.7)	1 (0.5)	3 (3.9)	3 (7.0)	8.7 (2.3, 33.6)**
Messages	8 (1.8)	6 (2.9)	5 (6.4)	9 (20.9)	6.3 (2.9, 14.0)*
Book/song solely for person	33 (7.3)	11 (5.4)	13 (16.7)	7 (16.3)	2.7 (1.5, 4.8)*
Influenced by strange force	18 (4.0)	7 (3.4)	7 (9.0)	5 (11.6)	2.9 (1.4, 5.8)**
Forced to move	11 (2.4)	4 (2.0)	4 (5.1)	6 (14.0)	4.0 (1.7, 9.3)*

[a]T2 and T3 associations tested jointly with data in the long format.
*$P \leq .001$; **$P \leq .01$; ***$P < .05$.

Table 4. Prevalence of Specific Hallucinations in Groups With (1) Any Hallucination but No Delusions (2) Combination of Any Delusion and Any Hallucination

	% With Specific Hallucination in Group With Any Hallucination but No Delusions, (*n*, %)		% With Specific Hallucination in Group With Combination of Any Hallucination With Any Delusion, (*n*, %)		
Psychotic Symptom	T2 (*n* = 39)	T3 (*n* = 26)	T2 (78)	T3 (43)	T2–T3,[a] OR (95% CI)
Seeing things	9 (23.1)	4 (15.4)	18 (23.1)	10 (23.4)	1.2 (0.6, 2.6)
Hearing things	11 (28.2)	10 (38.5)	29 (37.2)	22 (51.2)	1.6 (0.8, 3.0)
Smelling things	8 (20.5)	6 (23.1)	18 (23.1)	11 (25.6)	1.2 (0.6, 2.4)
Tasting things	9 (23.1)	5 (19.2)	17 (21.8)	11 (25.6)	1.0 (0.5, 2.2)
Feeling things	9 (23.1)	7 (26.9)	27 (34.6)	14 (32.6)	1.6 (0.8, 3.3)

[a]T2 and T3 associations tested jointly with data in the long format.

other groups (delusions only: 10.5%, hallucinations only: 13.9%, reference group: 3.0%; table 7). A directionally similar but much more attenuated pattern was apparent for persistence of negative symptoms (table 8).

Family History and Nongenetic Risk Factors

The group with delusions and hallucinations consistently had the highest level of parental psychopathology, although differences between groups were mostly not statistically significant (table 9).

A similar pattern, with more contrast between the groups, was apparent for the nongenetic risk factors, with the clearest result for childhood trauma. The rate of trauma exposure for individuals with delusions and hallucinations was 34.7%, significantly higher than the rates observed in individuals with delusions only (23.8%), hallucinations only (13.9%), and the reference group (18.3%). A similar pattern was observed for the other exposures (table 10).

Discussion

Main Findings

Co-occurrence of Delusions and Hallucinations. At the level of the general population, the combination of delusional ideation and hallucinatory experiences co-occurred more often than would be expected by chance, which points to the direction of a fundamental unifying mechanism, independent of illness, hereafter referred to as ''hallucinatory–delusional syndrome.'' Furthermore, the pattern of results in tables 3 and 4 indicates that

Table 5. Indicators of Impact on Functioning and Caseness

	Help-Seeking %, (*n*/*N*)	OR (95% CI)	Dysfunction %, (*n*/*N*)	OR (95% CI)	Thinking about death %, (*n*/*N*)	OR (95% CI)	Caseness %, (*n*/*N*)	OR (95% CI)
T2–T3 no psychotic symptoms, (*n* = 3892)	0.1% (5/3892)	1[a]	0.0%	—[b]	22.4% (554/2479)	1[a]	1.2% (45/3887)	1[a]
T2–T3 isolated hallucinations, (*n* = 65)	7.7% (5/65)	69.1 (19.4, 246.0)*	32.3% (21/65)	1[a]	31.3% (15/48)	1.5 (0.8, 2.8)	3.1% (2/65)	2.7 (0.7, 11.6)
T2–T3 isolated delusions, (*n* = 656)	8.7% (57/656)	76.7 (30.6, 192.5)*	35.8% (235/656)	1.2 (0.7, 2.0)	34.8% (138/397)	1.8 (1.5, 2.3)*	7.0% (46/656)	6.7 (4.4, 10.2)*
T2–T3 hallucinations and delusions, (*n* = 121)	35.5% (43/121)	466.1, (178.8, 1215.1)*[c,d]	57.9% (70/121)	2.9 (1.5, 5.4)[c,d]	57.3% (51/89)	4.5 (2.9, 7.1)*[c,d]	20.7% (25/121)	23.4 (13.9, 39.5)*[c,d]

Note: Help-seeking: informing a doctor about the psychotic symptoms, dysfunction: effect on daily life functioning of psychotic symptoms, caseness: clinical rating of problems with mental health.
[a]Reference category.
[b]OR = infinite.
[c]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated hallucinations, $P < .01$.
[d]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated delusions, $P < .001$.
*$P \leq .001$.

Table 6. Comorbid Psychopathology

	Negative Symptoms %, (*nl/N*)	OR (95% CI)	Depressive Symptoms Mean (SD)	OR (95% CI)	Manic Symptoms Mean (SD)	OR (95% CI)	Any Anxiety Disorder %, (*nl/N*)	OR (95% CI)	Any Drug Used More Than 5 Times %, (*nl/N*)	OR (95% CI)	Alcohol Abuse or Dependence %, (*nl/N*)	OR (95% CI)
T2–T3 no psychotic symptoms, (n = 3892)	11.7% (454/3890)	1[a]	1.1 (1.6)	1[a]	0.3 (0.7)	1[a]	14.2% (551/3892)	1[a]	21.9% (843/3859)	1[a]	12.2% (475/3892)	1[a]
T2–T3 isolated hallucinations, (n = 65)	15.4% (10/65)	1.3 (0.7, 2.6)	2.1 (2.1)	1.4 (1.2, 1.6)*	0.8 (1.1)	1.8 (1.4, 2.2)*	26.2% (17/65)	2.2 (1.2, 4.0)**	38.5% (25/65)	2.3 (1.4, 3.9)**	26.2% (17/65)	2.8 (15, 5.1)**
T2–T3 isolated delusions, (n = 656)	16.0% (105/656)	1.4 (1.1, 1.7)**	1.7 (2.0)	1.2 (1.2, 1.3)*	0.7 (1.1)	1.6 (1.5, 1.8)*	21.7% (142/656)	1.8 (1.5, 2.3)*	31% (202/652)	1.5 (1.3, 1.9)*	24.2% (159/656)	2.2 (1.8, 2.8)*
T2–T3 hallucinations and delusions, (n = 121)	21.5% (26/121)	2.0 (1.3, 3.0)**	2.6 (2.2)	1.6 (1.4, 1.8)*[b]	1.1 (1.3)	2.2 (1.9, 2.6)*[b]	45.5% (55/121)	5.8 (3.9, 8.6)*[b,c]	39.3% (46/117)	2.3 (1.6, 3.4)*	36.4% (44/121)	4.3 (2.9, 6.5)*[b]

Note: Negative symptoms: absence or presence of any negative symptoms, depressive symptoms: continuous sum score of number of depressed symptoms, manic symptoms, continuous sum score of number of manic symptoms.
[a]Reference category.
[b]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated delusions, $P < .01$.
[c]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated hallucinations, $P < .01$.
*$P \leq .001$; **$P \leq .01$.

delusional content is contingent on the presence of hallucinations, whereas type of hallucination is not contingent on presence of delusions, suggesting delusions may represent a cognitive response to hallucinations and a deepening of the psychotic state, in agreement with earlier theories formulated by Maher and Ross and, more recently, Kapur.[21–24] These findings, combined with the fact that the group with only hallucinations tended to show the weakest difference with the nonpsychotic group, support the notion that a specific subgroup of the population is at risk of worsening of psychosis through secondary delusion formation, given hallucinatory experiences, and that delusion formation may be associated with affective predisposition and nongenetic risk factors.

Delusions, Hallucinations, and Other Perceptual Anomalies. A number of issues need explaining. First, the rate of hallucinations was much lower than delusions. An unlikely explanation is that most delusions represent false positives and most hallucinations true positives, given the fact that the clinical relevance of isolated delusions was greater than isolated hallucinations. A more likely (partial) explanation is that the M-CIDI measures for delusions are more sensitive and numerous than those for hallucinations and, additionally, that a range of more subtle, ''basic''[49,50] perceptual anomalies can occur in the early phases of psychosis that are not picked up by the M-CIDI. This would also explain why, on most measures, isolated delusions impacted more on measures of clinical severity than isolated hallucinations.

Second, the fact that certain, mostly ''first-rank-type'' delusions were more specifically associated with hallucinations than others suggests that delusions ''follow'' hallucinations but also that the content of secondary delusional ideation is not random, and often takes on the form of altered self-representation and social inference, resulting in experience of thought alienation, passivity-like experiences and paranoia. To the degree that hallucinations are at the severest end of perceptual anomalies associated with psychosis, it may be hypothesized that other types of delusions, that in this study were less ''comorbid'' with hallucinatory experiences, represent cognitive schemes associated with less severe perceptual anomalies that are not picked up by the M-CIDI.

The Hallucinatory–Delusional Syndrome as a Predictor of Clinical Outcomes. Furthermore, the results showed that the combination of hallucinations and delusions, compared with either one in isolation, may represent an important intermediate step toward transition to (1) persistence of symptoms and (2) clinical outcomes, which may be mediated, to a degree, by negative symptoms[43] and by higher rates of comorbid nonpsychotic psychopathology or familial liability to nonpsychotic psychopathology, particularly parental mania, conform earlier observations.[33,35,51,52]

Table 7. Persistence of Positive Symptoms

	10-Year Psychosis Persistence (T0–T3)[a] %, (*n*, *N*)				
	Never	Once	Twice	Thrice	OR (95% CI)
T2–T3 no psychotic symptoms, (*n* = 3892)	84.5% (3290/3892)	12.5% (487/3892)	2.7% (105/3892)	0.3% (10/3892)	1[b]
T2–T3 isolated hallucinations, (*n* = 65)	61.5% (40/65)	24.6% (16/65)	13.9% (9/65)	0.0% (0/65)	2.3 (1.7, 3.2)*
T2–T3 isolated delusions, (*n* = 656)	69.1% (453/656)	20.4% (134/656)	8.7% (57/656)	1.8% (12/656)	2.0 (1.7, 2.3)*
T2–T3 hallucinations and delusions, (*n* = 121)	52.9% (64/121)	22.3% (27/121)	16.5% (20/121)	8.3% (10/121)	3.3 (2.7, 4.2)*[c,d]

[a]Persistence of positive symptoms was measured at T0, T2, and T3 and derived from the SCL-90R. Persistence of positive psychotic symptoms was expressed as how often they occurred during the 3 different interview waves.
[b]Reference category.
[c]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated hallucinations, $P < .05$.
[d]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated delusions, $P < .001$.
*$P \leq .001$.

The Hallucinatory–Delusional Syndrome as an Outcome of Nongenetic Risk Factors. The results suggest that environmental risk factors for psychotic illness may act in part by increasing the risk of delusional ideation in individuals experiencing perceptual alterations. This would go some way toward explaining why associations between childhood trauma and either hallucinations or delusions have been inconsistent.[53]

A Two-Stage Hallucinatory–Delusional Syndrome Underlying Psychotic Illness

The findings suggest that the early stages of psychosis may involve perceptual anomalies perceived as hallucinations that, if complicated by delusional ideation under the influence of environmental risks and (liability for) affective dysregulation, give rise to a hallucinatory–delusional syndrome that is associated with a higher probability of persistence of psychotic symptoms and transition to clinical psychotic disorder. Thus, identifying the group of patients with first-stage early perceptual alterations may lead to expanded insight and knowledge about the premorbid stages of psychosis, particularly if more is known about second-stage onset of delusional ideation. Few studies have focused on the onset of delusional formation following hallucinatory experiences. Two studies reported that in those with hallucinations, voice characteristics and the level of distress[28] they generate, in a context of affective dysregulation and negative schemata associated with childhood trauma, may increase the risk for secondary delusion formation.[27] Another study found that in the general population, trauma impacts on delusion formation through an affective pathway.[54]

Limitations and Methodological Issues

The data presented in the current article were gathered in a large epidemiological study; therefore, instruments and tools used were not refined with regard to the hypotheses under investigation. Second, follow-ups were infrequent, precluding the investigation of the dynamic relationship between delusions and hallucinations over time. Therefore, although the data suggest that hallucinations may be followed by delusional ideation, an alternative explanation is that delusions are a cross-sectional indicator of the severity of the underlying process that also affects perceptual alterations. While this would also be an important observation, it differs substantially from the more dynamic interpretation given above. Therefore, more fine-grained follow-up work is necessary. Third,

Table 8. Persistence of Negative Symptoms

	10-Year Negative Symptom Persistence (T0–T3)[a] %, (*n*, *N*)				
Never	Never	Once	Twice	Thrice	OR (95% CI)
T2–T3 no psychotic symptoms, (*n* = 3359)	72.2% (2425/3359)	23.6% (794/3359)	3.7% (124/3359)	0.5% (16/3359)	1[b]
T2–T3 isolated hallucinations, (*n* = 54)	68.5% (37/54)	22.2% (12/54)	9.3% (5/54)	0.0% (0/54)	1.2 (0.8, 1.9)
T2–T3 isolated delusions, (*n* = 556)	65.8% (366/556)	27.0% (150/556)	6.1% (34/556)	1.1% (6/556)	1.2 (1.1, 1.5)*
T2–T3 hallucinations and delusions, (*n* = 94)	59.6% (56/94)	30.9% (29/94)	9.6% (9/94)	0.0% (0/94)	1.5 (1.1, 2.0)**

[a]Persistence of negative symptoms was measured at T0, T2, and T3 and derived from the M-CIDI. Persistence of negative symptoms was expressed as how often they occurred over the 3 different interview waves.
[b]Reference category.
*$P \leq .01$; **$P \leq .05$.

Table 9. Family History[a]

	Parental Alcohol/ Substance Misuse %, (*n*/*N*)	OR (95% CI)	Parental Depressive Symptoms Mean (SD)	OR (95% CI)	Parental Manic Symptoms Mean (SD)	OR (95% CI)
T2–T3 no psychotic symptoms, (*n* = 1483)	21.0% (310/1483)	1[b]	2.0 (2.1)	1[b]	0.3 (0.8)	1[b]
T2–T3 isolated hallucinations, (*n* = 27)	29.6% (8/27)	1.6 (0.7, 3.7)	2.6 (2.2)	1.1 (0.9, 1.4)	0.2 (0.6)	0.8 (0.4, 1.4)
T2–T3 isolated delusions, (*n* = 241)	26.6% (64/241)	1.4 (1.0, 1.9)	2.1 (2.1)	1.0 (0.9, 1.1)	0.3 (0.8)	1.0 (0.8, 1.2)
T2–T3 hallucinations and delusions, (*n* = 36)	38.9% (14/36)	2.4 (1.2, 4.9)*	2.3 (2.2)	1.1 (0.9, 1.3)	0.7 (1.1)	1.5 (1.1, 2.1)*[c]

[a]Family history was only assessed at T1, therefore only data of the younger sample (14–17 years at T0) was included in these analyses.
[b]Reference category.
[c]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated delusions, $P < .05$.
*$P \leq .05$.

no formal diagnoses were used for psychotic disorder. The reason for this is that in general population samples, diagnoses are less sensitive than multiple indicators of help-seeking, dysfunction, and caseness, that better reflect the dimensional nature of the largely subsyndromal expression of psychosis. Fourth, the measure of psychosis persistence was based on SCL-90R self-report measures. Although analyses against the interview-based M-CIDI measures of psychotic symptoms suggested convergent and discriminant validity, self-report may have generated false positive psychotic experiences, increasing random error. Nevertheless, a substantial amount of literature exists on the validity of self-reported psychotic symptoms, SCL-90R and other instruments, suggesting acceptable validity and reliability.[5,55–57]

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Table 10. Nongenetic Risk Factors

	Trauma at t0 %, (*n*/*N*)	OR (95% CI)	Cannabis Use More Than 5 Times at T0, (*n*/*N*)	OR (95% CI)	Urbanicity T0 %, (*n*/*N*)	OR (95% CI)
T2–T3 no psychotic symptoms, (*n* = 3982)	18.3% (711/3982)	1[a]	12.0% (450/3764)	1[a]	69.8% (2716/3892)	1[a]
T2–T3 isolated hallucinations, (*n* = 65)	13.9% (9/65)	0.8 (0.4, 1.6)	17.8% (11/62)	1.9 (1.0, 3.7)	76.9% (50/65)	1.4 (0.8, 2.6)
T2–T3 isolated delusions, (*n* = 656)	23.8% (156/656)	1.5 (1.2, 1.8)*	17.9% (113/632)	1.8 (1.4, 2.3)*	72.7% (477/656)	1.2 (1.0, 1.4)
T2–T3 hallucinations and delusions, (*n* = 121)	34.7% (42/121)	2.6 (1.7, 4.0)*[b,c]	20.5% (24/117)	2.3 (1.4, 3.8)**	76.9% (93/121)	1.5 (0.9, 2.2)

[a]Reference category.
[b]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated hallucinations, $P < .01$.
[c]OR T2–T3 hallucinations and delusions > OR T2–T3 isolated delusions, $P < .01$.
*$P \leq .001$; **$P \leq .01$.

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