Nonaffective Psychosis After Prenatal Exposure to Rubella

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Objective: The authors' goal was to investigate the suggestion of previous investigations that prenatal viral exposures might increase the later risk of psychotic disorders. **Method:** They conducted a follow-up study in young adulthood of a birth cohort that was previously documented, by clinical examination and serological testing, to have in utero rubella exposure during the 1964 rubella epidemic. Data were also obtained from an unexposed birth cohort and from the Epidemiological Catchment Area survey. Young adult subjects were administered a standard psychiatric diagnostic interview. The authors compared the proportions of subjects with nonaffective psychosis in the exposed and unexposed cohorts. **Results:** The rubella-exposed subjects, most of whom were exposed in the first trimester, demonstrated a substantially greater risk for nonaffective psychosis than the subjects who were not exposed to rubella (relative risk=5.2). **Conclusions:** There is an association between clinically and serologically diagnosed prenatal viral infection and nonaffective psychosis in adulthood.

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Although there has long been speculation that prenatal viral infection plays a role in the development of psychotic disorders (1), only recently have there been attempts to examine this question empirically. In the present report, we examine the relation between prenatal exposure to rubella virus, documented prospectively, and nonaffective psychosis in adulthood.

Studies on the role of gestational viral infection as a cause of psychotic disorders have been controversial and contradictory. Some ecological studies (2, 3) have demonstrated higher rates of psychosis among individuals exposed in the second trimester of pregnancy during influenza epidemics, but others (4, 5) have failed to detect such an association. These discrepant findings may be a result of the use of ecological data on exposure rather than confirmed infection in individual pregnancies. In addition, most previous studies have not examined relationships between in utero exposure to other viral agents and risk of psychosis.

Among other viruses, evidence suggests that rubella is a plausible agent in the etiology of nonaffective psychosis. Rubella was one of the first viruses demonstrated to cause congenital anomalies after gestational exposure (6), and, more than 50 years since this discovery, it remains a model for viral teratogenic effects on the central nervous system. Of particular relevance to psychiatric disorders, congenital rubella has clear developmental manifestations involving the nervous system, including hearing defects, mental retardation, ventriculomegaly, encephalitis, cataracts (7), and, possibly, childhood psychiatric disorders such as autism, separation anxiety, and impaired social relations (8).

The present study is a follow-up of a birth cohort in which individual members were prospectively documented to have been exposed to rubella virus in utero. In 1971, Chess and colleagues (8) reported on a study of childhood psychiatric disorders in a sample of children enrolled in the Rubella Birth Defects Evaluation Project, which was begun after the 1964 rubella epidemic in New York City. In all of these individuals, maternal rubella infection was clinically diagnosed during pregnancy, and in the majority, viral exposure was serologically documented by antibody studies.

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In this follow-up investigation of nonaffective psychosis in young adults with normal intelligence from this birth cohort, we administered a comprehensive, research-based psychiatric diagnostic interview. The study had three main advantages: 1) the subjects' viral exposure status was prospectively documented, through clinical diagnosis and serological measures, 2) standardized psychiatric diagnostic assessments were administered blind to the study hypotheses, and 3) community samples of unexposed individuals were available for comparison. Since a lay interview was used, we selected nonaffective psychosis as our main diagnostic outcome because the correspondence between lay and clinical interview diagnoses was better for this broader outcome than for schizophrenia (9, 10). We compared the proportion of subjects with nonaffective psychosis in the rubella-exposed birth cohort in young adulthood with the proportion in an age-matched comparison group of subjects who had not been exposed to rubella in utero. For further confirmation, we compared our results with those from a large, cross-sectional community study.

METHOD

Description of Birth Cohorts

Exposed cohort. The exposed cohort was that of the Rubella Birth Defects Evaluation Project, which was begun in 1964 during a major rubella epidemic in the New York City area and followed up by Dr. Chess from early childhood and by Dr. Cohen until young adulthood (8).

The Rubella Birth Defects Evaluation Project was established at New York University Medical Center in 1964. Its main objective was to examine the clinical manifestations of congenital rubella and develop appropriate management techniques (8, 11). For this purpose, announcements and bulletins were disseminated to physicians throughout New York City requesting referrals for pregnant mothers suspected of having rubella as well as for infants with signs of congenital rubella syndrome. For 243 of the children enrolled in the Rubella Birth Defects Evaluation Project, either the mothers were clinically diagnosed with rubella during pregnancy or the infants were diagnosed with congenital rubella. Serological confirmation of infection was obtained in the majority of both mothers and infants. This birth cohort received psychiatric, intellectual, behavioral, and psychosocial evaluations during childhood, adolescence, and young adulthood (age 21–23 years).

Evaluation of the 214 subjects who participated in the adolescent follow-up assessment revealed a number of mental and physical handicaps, including mental retardation (N=67 [31%]), severe/moderate hearing loss (N=176 [82%]), and blindness (N=36 [17%]). As a result, the types of assessments administered at the young adult follow-up were tailored to the capacities of each individual. Toward this end, the cohort was divided into three main groups. The first group (N=106) consisted of individuals with severe and multiple handicaps, often consisting of mental retardation (IQ less than 70), blindness, and deafness within the same individual. The children in the second group had an IQ of 70 or more and deafness but no other major physical or mental handicaps, and the third group had neither deafness nor other handicaps. The 137 subjects in the latter two groups were targeted for a structured psychiatric assessment (described in the section on Diagnostic Assessments) because the multiple handicaps of the subjects in the first group seriously compromised their ability to provide valid responses to the symptom items of this instrument. The exclusion of subjects with multiple handicaps from the diagnostic interview would likely introduce conservative error because the prominent developmental brain damage in these subjects would tend to increase, rather than decrease, the risk of psychosis.

Unexposed sample: Albany/Saratoga. The Albany/Saratoga unexposed cohort was derived from a community-based longitudinal study of factors affecting physical and psychological health of children and young adults. This cohort was described in detail by Cohen and Cohen (12). The cohort was randomly sampled in 1975 in Albany and Saratoga County, N.Y., an area selected for its diversity in terms of socioeconomic status, urban versus rural residence, and social problems. These two counties are in upstate New York and represented a population that was one-fourth urban, one-fourth rural, and one-half suburban. The members of this cohort, selected for the current comparison to be of equivalent age to the cohort exposed to rubella, were born between 1967 and 1973. Given the rarity of rubella infection during this time period (estimated to be less than 0.1%), it can be safely assumed that virtually the entire cohort was not exposed to the virus during gestation.

Individuals in the unexposed cohort received assessments during childhood, adolescence, and adulthood. At the young adult follow-up, the cohort included 766 individuals (78% retrieval rate). For the present study, we selected from this cohort those subjects who most closely matched the exposed subjects in age (21–23 years) (N=180).

U.S. Epidemiological Catchment Area Study (ECA). The methods of the ECA have been elaborated in detail elsewhere (13) and will be described only briefly here. This study was conducted from 1980 to 1984 and included a probability sample of more than 18,000 adults, age 18 and older, living in five U.S. communities (New Haven, Conn.; Baltimore; St. Louis; Piedmont County, N.C.; and Los Angeles). All except the North Carolina site were urban locations. Census blocks and households served as sampling units, and one adult from each sample household was selected by using a procedure that provided a random selection of all adults within each household (14). The response rate was 75%.

For the present study, the ECA unexposed sample was derived by restricting the age range of subjects to 21–23 years to correspond to the ages of the rubella-exposed and Albany/Saratoga cohorts. The subjects were born between 1957 and 1960 and interviewed in 1980. This procedure resulted in a sample size of 1,346. Because exposure to rubella is rare during pregnancy, it can be assumed that virtually the entire ECA sample was unexposed.

Written informed consent was obtained from all subjects after a full explanation of the procedure.

Diagnostic Assessments

The members of the rubella-exposed birth cohort received a modified version of the Diagnostic Interview Schedule for Children (15), a comprehensive diagnostic interview covering all major psychiatric symptoms in accord with DSM-III-R. The Diagnostic Interview Schedule for Children was selected for this follow-up because one major aim of the study was to examine the course of childhood disorders (e.g., attention deficit hyperactivity disorder) into young adulthood. Nonetheless, the items regarding psychotic and other major psychiatric disorders in the Diagnostic Interview Schedule for Children are very similar to those in the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (16) because they are both based on DSM criteria. The Diagnostic Interview Schedule for Children was administered between 1985 and 1988 (17). In order to be sure that the questions were the same for the deaf and nondeaf members of the cohort, the Diagnostic Interview Schedule for Children was administered by computer with a skilled sign interpreter at hand for the deaf subjects.

The Albany/Saratoga unexposed cohort also received the Diagnostic Interview Schedule for Children. These interviews were administered between 1990 and 1993. Data from the Diagnostic Interview Schedule for Children were available for 164 of the 180 subjects.

The ECA sample was administered the DIS (16), a fully structured interview schedule covering all major psychiatric symptoms, in accord with DSM-III criteria. Although the DIS was developed for the application of DSM-III rather than DSM-III-R criteria, this interview included questions nearly identical in wording to questions in the Di-

TABLE 1. Characteristics and Rates of Nonaffective Psychosis in Cohorts of Subjects Who Were or Were Not Exposed to Rubella in Utero

Characteristic and Diagnosis	Rubella-Exposed Subjects (N=70)		Unexposed Subjects in Albany/ Saratoga Study (N=164)[a]		Unexposed Subjects in Epidemiologic Catchment Area (ECA) Study (N=1,346)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)	22	0.6	22	0.5	22	1.1
	N	%	*N*	%	*N*	%
Male sex	35	50.0	85	51.8	580	43.1
White ethnicity	52	74.3	150[b]	92.6	696	51.7

[a] Diagnostic data missing for 16 of the 180 subjects in the Albany/ Saratoga unexposed cohort.
[b] Ethnicity status available for only 162 subjects.

agnostic Interview Schedule for Children for virtually all of the diagnostic items used in the present study. The DIS was also administered by lay interviewers.

Definition of Outcome

The outcome explored in the present study was nonaffective psychosis. This diagnosis was defined as 1) at least one psychotic symptom (delusions and/or hallucinations) for a minimum of 6 months; 2) no evidence of a major affective disorder (bipolar or unipolar) by DSM-III-R criteria concurrent with the psychosis; and 3) no evidence that a medical condition or substance use initiated or maintained the psychosis.

Statistical Analysis

We compared the rubella-exposed cohort with the Albany/Saratoga unexposed cohort and the ECA unexposed sample with regard to the proportion of each sample with nonaffective psychosis as defined. Relative risks (with corresponding 95% confidence intervals [CIs]) comparing the rubella-exposed cohort with the Albany/ Saratoga unexposed group and the ECA unexposed group were calculated. The relative risk was considered to be statistically significant if the lower boundary of the 95% CI excluded unity (1.0). Statistical significance was also tested by using chi-square and Fisher's exact tests when appropriate; all statistical tests were two-tailed.

RESULTS

Of the 137 subjects in the rubella-exposed cohort who were targeted for assessment as young adults, 70 (51%) were located and interviewed in young adulthood. These 70 subjects constitute the exposed cohort for the present study; 41 (58.6%) of these subjects had severe/profound deafness, 11 (15.7%) had hearing impairment, and 18 (25.7%) had normal hearing.

Demographics

The demographic data for the exposed and unexposed subjects are presented in table 1. With respect to age and sex, the rubella-exposed cohort was highly similar to the Albany/Saratoga and the ECA unexposed groups. With regard to ethnicity, however, the exposed cohort had a significantly smaller proportion of white subjects than the Albany/Saratoga unexposed group (χ^2=12.3, df=1, p<0.001) and a significantly greater proportion of white subjects than the ECA unexposed group (χ^2=13.6, df=1, p<0.001) (table 1).

Comparison of Diagnostic Outcomes

We found a significantly higher proportion of subjects with nonaffective psychosis (p<0.001, Fisher's exact test), all of whom were of normal intelligence, in our rubella-exposed subjects (11 [15.7%] of 70) than in the Albany/Saratoga unexposed subjects (five [3.0%] of 164) (relative risk=5.2, 95% CI=1.9–14.3) and the ECA unexposed subjects (13 [1.0%] of 1,346) (relative risk=16.3, 95% CI=7.6–35.0).

Potential Confounders and Mediators

Two potential confounders and/or mediators in the present study are deafness and ethnicity because each is associated with exposure to rubella; the rate of deafness was 59% (N=41) in the exposed subjects, compared with virtually zero in the unexposed subjects. There were also significant ethnicity differences between the exposed group and both unexposed groups (table 1). Moreover, each of these factors has been associated with higher rates of psychosis (18). We therefore examined whether each of these factors could have confounded or mediated our results.

Deafness. We divided the rubella-exposed cohort into three groups: deaf (N=41), hearing impaired (N= 11), and normal hearing (N=18). In the deaf and normal-hearing groups, the proportions of subjects with nonaffective psychosis were nearly identical (seven [17.1%] and three [16.7%], respectively) and were slightly higher than the proportion with nonaffective psychosis for the entire exposed cohort (11 [15.7%]). In the hearing-impaired group, one subject (9.1%) had nonaffective psychosis.

Ethnicity. We compared the respective proportions of subjects with nonaffective psychosis between the exposed and unexposed groups by ethnicity status. Within the subgroup of white subjects, we observed a significantly higher proportion of subjects with nonaffective psychosis in the exposed cohort than in the Albany/Saratoga unexposed group (seven [13.5%] of 52 versus five [3.3%] of 150) (relative risk=3.8, 95% CI= 1.26–11.5, p=0.02, Fisher's exact test). For nonwhite subjects, the proportion with nonaffective psychosis was also higher in the exposed versus the unexposed (four [22.2%] of 18 versus none of 12).

Potential for Selection Bias

As noted, 67 (48.9%) of 137 subjects targeted for interview were lost to follow-up. Because this may have introduced selection bias, we conducted a sensitivity analysis. Even if none of the subjects lost to follow-up had nonaffective psychosis, the proportion with nonaffective psychosis would have been 11 (8.0%) of 137 exposed subjects and five (3.0%) of 164 unexposed

subjects (relative risk=2.6, 95% CI=0.94–7.40, p= 0.06, Fisher's exact test).To further address the potential effect of loss to follow-up on our findings, we restricted the analysis to subjects in the highest two socioeconomic classes because the follow-up rate was considerably higher in these two classes (26 [63.4%] of 41 overall) than in the other classes (44 [45.8%] of 96 overall). Among the 26 subjects in the higher social classes, six (23.1%) had nonaffective psychosis. This figure is higher than the proportion of subjects with nonaffective psychosis in the entire exposed cohort. The fact that the effect persisted in a subgroup with a relatively high rate of follow-up argues further against selection bias as a cause of our finding.

Relationship to Nonaffective Psychosis of Gestational Timing of Rubella Infection and Antibody Titers

The respective frequencies of individuals exposed to rubella in each gestational month (based on reported month of clinical infection in the mother) for the subjects with and without nonaffective psychosis are presented in table 2. In both groups, the vast majority of subjects were exposed to rubella in the first trimester. The proportions exposed in each month of gestation were similar between the two groups.

TABLE 2. Gestational Month of Maternal Infection in Rubella-Exposed Subjects With and Without Nonaffective Psychosis[a]

Gestational Month of Infection	Subjects With Nonaffective Psychosis (N=9)		Subjects Without Nonaffective Psychosis (N=42)	
	N	%	N	%
1	1	11.1	2	4.8
2	2	22.2	11	26.2
3	4	44.4	16	38.1
4	2	22.2	9	21.4
5	0	0.0	3	7.1
6	0	0.0	1	2.4
>6	0	0.0	0	0.0

[a] Data on the gestational month of maternal infection were unavailable for two of the 11 subjects with nonaffective psychosis and 17 of the 59 subjects without nonaffective psychosis.

DISCUSSION

We have demonstrated a higher risk of nonaffective psychosis in a birth cohort of individuals of normal intelligence who were prospectively documented to have in utero exposure to rubella than in a birth cohort who were not exposed to rubella. Although we focused on the broader outcome of nonaffective psychosis rather than on specific diagnoses, this outcome would have included the following DSM-III-R diagnoses: schizophrenia, delusional disorder, and psychotic disorder not otherwise specified. These findings did not appear to be confounded or mediated by deafness or ethnicity and are not likely to be explained by selection bias (as discussed in the Limitations section).

Our findings are consistent with the results of a 50-year follow-up study of 50 subjects with well-documented congenital rubella from Sir Norman Gregg's original birth cohort (19). Two (4%) of his 50 subjects received a diagnosis of schizophrenia.

Although no associations were demonstrated in two previous epidemiologic studies of prenatal exposure to rubella epidemics and psychotic disorders (20, 21), these studies were limited by the use of ecologic data and by uncertainty with respect to rubella exposure. In contrast, the data of the present study possess a high degree of accuracy with respect to the exposure, the timing of maternal infection was prospectively documented, and serological evidence of infection was demonstrated in infants and their mothers. The detection during infancy of immunoglobulin m-specific rubella antibody, which can be produced only by the fetus, combined with documented maternal infection at the time of pregnancy, is strong evidence that in utero rubella exposure occurred.

The careful documentation of the timing of maternal infection also permitted us to evaluate the relation between rubella exposure during specific periods of gestation and the risk of nonaffective psychosis. In this regard, we demonstrated that the vast majority of cases of nonaffective psychosis were initially exposed during the first trimester, similar to the proportion exposed in the entire cohort. These findings are particularly salient in the light of our demonstration of an association between prenatal famine exposure during early gestation and schizophrenia in adulthood (22).

Plausibility of the Association

Rubella is a plausible causal agent for nonaffective psychosis (1). This virus remains the best documented infectious exposure to cause fetal neurodevelopmental defects, including sensorineural deafness, mental retardation, cerebral palsy, and, possibly, autism. Thus, the findings of the present study suggest that nonaffective psychosis is yet another neuropsychiatric sequela of prenatal rubella. In this regard, we wish to emphasize that nonaffective psychosis occurred independently of these other neurodevelopmental consequences: the risk was similar in nondeaf subjects, and all of the subjects studied were free of mental retardation, neurological disorders, and autism.

These findings are consistent with the strong predilection of rubella for neural tissue (23). The virus first infects the placenta, usually leading to direct fetal infection, and then invades the fetal brain, disrupting organogenesis and causing an encephalitis. In addition, a magnetic resonance imaging study (24) demonstrated that subjects with congenital rubella and schizophrenia-like symptoms had reduced cortical gray matter and greater size of the lateral ventricles, findings that have been shown in studies of schizophrenia.

Implications

Given the precision with which prenatal rubella exposure was documented in the present study and an

extensive literature on its central nervous system teratogenicity, this virus may provide a model for other gestational viral infections as possible causes of schizophrenia-like neurodevelopmental disorders. Higher rates of adult nonaffective psychoses have also been reported among individuals who were in utero during epidemics of measles and varicella zoster (20) and among subjects who were exposed neonatally to neurological infections (25). Although rubella has been nearly eliminated in the industrialized world since the introduction of rubella vaccine in 1969, rubella epidemics remain a major public health problem in third-world countries. Increased awareness of later psychiatric sequelae of the infection may further worldwide efforts toward its elimination.

Limitations

Selection bias. The limitations of the present study include possible selection bias from loss to follow-up or from inclusion of gravidas with potential risk factors for nonaffective psychosis in the Rubella Birth Defects Evaluation Project cohort. The first source of selection bias may have stemmed from the fact that loss to follow-up of subjects without mental retardation or major physical handicaps from adolescence (ages 12–15 years) to young adulthood (ages 21–23 years) was nearly 50% in the rubella-exposed cohort but only 22% over a comparable period in the unexposed subjects. If healthier subjects were more likely to be lost to follow-up, our findings could have been biased. However, we showed that a subsample of rubella-exposed subjects with a better rate of follow-up (63%)—those in the highest two social classes—also had significantly higher proportions of subjects with nonaffective psychosis. Furthermore, we demonstrated in a sensitivity analysis (discussed in the Results section) that the association between prenatal rubella and schizophrenia could not be accounted for by loss to follow-up.

The second source of selection bias may have emerged if gravidas with risk factors for nonaffective psychosis, especially a history of mental illness or extreme poverty, were preferentially selected into the Rubella Birth Defects Evaluation Project cohort. However, the ascertainment procedures (discussed in the Method section) provide no evidence that this would have occurred, at least to any substantial degree. In addition, with regard to extreme poverty as a source of selection bias, we demonstrated that the risk of nonaffective psychosis was higher in subjects from the two highest social classes than in the entire cohort (discussed in the Potential for Selection Bias section). Moreover, socioeconomic status of origin was widely distributed in the Rubella Birth Defects Evaluation Project cohort: 61% of the subjects were in the highest three social classes and only 20% in the lowest social class. Thus, these results do not support selection bias as a sufficient explanation of our results. Nonetheless, the difficulty of defining the true source population from which the cases were derived limits the ability to fully address this issue.

Validity of diagnoses. A second limitation concerns the validity of diagnoses based on the Diagnostic Interview Schedule for Children. We addressed this issue in three ways. First, we used a broader outcome—nonaffective psychosis—for which the correspondence between diagnoses generated from clinical and lay interviews is better than for schizophrenia per se (9, 10). We also analyzed the results using schizophrenia as the outcome. We found that the proportions of subjects fulfilling criteria for schizophrenia were five (7.1%) of 70 in the exposed group compared with one (0.6%) of 164 in the Albany/Saratoga unexposed group (relative risk= 11.7, 95% CI=1.4–98.5, p=0.01, Fisher's exact test).

Second, we validated the diagnoses of nonaffective psychosis for some of the subjects in this birth cohort. In a study now underway, these subjects, who are now 34–35 years old, are receiving clinical psychiatric assessments with the Diagnostic Interview for Genetic Studies, an orally administered standardized psychiatric diagnostic instrument. The rater was blind to the previous results. Thus far, we have assessed four individuals who had been diagnosed with nonaffective psychosis according to the Diagnostic Interview Schedule for Children; preliminary results indicate that three of these subjects were also diagnosed with nonaffective psychosis according to the Diagnostic Interview for Genetic Studies (unpublished data).

Third, to further address the issue of diagnostic validity, we compared the rubella-exposed and Albany/Saratoga unexposed cohorts with respect to panic disorder, a psychiatric illness that has not been postulated as being associated with prenatal rubella. Panic disorder was found in none of the 70 rubella-exposed, one (0.6%) of the 164 Albany/Saratoga unexposed, and 13 (1.0%) of the 1,346 ECA unexposed subjects. These similar rates argue against excessive false positive reports of symptoms in the exposed subjects as an explanation for our findings.

Another issue regarding diagnostic validity is whether our subjects with nonaffective psychoses may instead have had borderline or schizotypal personality disorder, which may feature transient psychotic symptoms. We consider this unlikely, at least for seven of our 11 subjects with nonaffective psychosis, who had either thought broadcasting or thought insertion—bizarre delusions that are not typically found in either of these personality disorders.

Deafness as a potential confounder. A third limitation is the possibility of confounding by deafness. The majority of exposed subjects were deaf, in contrast to the unexposed, and a possible causal relation between deafness and psychosis has been hypothesized (18). However, we found nearly identical rates of nonaffective psychosis between the deaf and normal-hearing rubella-exposed subjects. These findings persisted whether the hearing-impaired group was included with the deaf or with the normal-hearing groups.

In addition, studies that have examined associations between deafness and psychosis are inconclusive. Although Altshuler and Sarlin (26) demonstrated a 2.5% prevalence of schizophrenia among hospitalized deaf subjects, they cited numerous factors that could have led to a spurious association, including selection bias and differences in diagnostic standards between deaf and hearing patients with schizophrenia. In another study, David et al. (18) found an association between severe hearing impairment in military inductees and later diagnoses of psychotic disorders, but the deafness could have been explained by intrauterine infections such as rubella.

Lack of knowledge of potential protective factors. The identification of factors that protected the rubella-exposed individuals from psychosis may be as important as the role of prenatal rubella in causing psychosis. Unfortunately, information on these factors is not readily available. Consequently, we are initiating of series of studies, including family history assessments and molecular genetic analyses, to address this question.

CONCLUSIONS

To our knowledge, this is the first study to show a relationship between serologically documented prenatal viral exposure and psychosis in adulthood. Careful analysis suggests that this association is not due to confounding, selection bias, or diagnostic misclassification. In view of the prospective nature of the study and the thorough documentation of both exposure and outcome, this finding provides a compelling rationale for future work on prenatal infectious exposures in the etiopathogenesis of nonaffective psychosis.

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