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ORIGINAL PAPER

Psychopathological correlates of the entorhinal cortical shape in schizophrenia

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Abstract Animal experiments have shown that early developmental lesions of the entorhinal cortex lead, after a prolonged interval, to an enhanced mesolimbic dopamine release and an increased locomotor activity in rats. Hence, disturbed shape of the entorhinal cortex might indicate maturational abnormalities relevant for psychotic symptoms in schizophrenia. We used an automated surface-based MRI method to perform a region of interest analysis of entorhinal cortical surface area, folding and thickness in 59 patients with schizophrenia and 59 healthy controls. We postulated the entorhinal cortical surface area, folding index, and thickness to be significantly smaller in patients with schizophrenia. Additionally, we expected the complexity of the entorhinal cortical shape to be associated with psychotic symptoms in schizophrenia. Our ROI analysis showed a significant thinner left entorhinal cortex. In addition, our data demonstrate a positive correlation between left entorhinal cortical surface area and folding index and severity of psychotic symptoms. In conclusion, we present new evidence for the involvement of the entorhinal cortex in the pathogenesis of schizophrenia. As cortical folding is a stable neuroanatomical parameter terminated in early neonatal stages, our data give reason to assume that the vulnerability to develop psychotic symptoms might be manifest at an early level of brain maturation.

Keywords Schizophrenia · Psychotic symptoms · Entorhinal cortex · Cortical surface area · Cortical folding · Cortical thickness

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Introduction

The entorhinal cortex constitutes the anterior portion of the medial temporal lobe. As a part of the temporolimbic system, the entorhinal area is known to represent a major gateway for the integration of multisensory information between neocortical areas and the hippocampus [1]. It might therefore play an important role in the pathophysiology of schizophrenia. Given the close anatomical connections between the entorhinal cortex and the hippocampus, which have been shown to be altered in schizophrenia both structurally [2] and functionally [3], this area is of high relevance for our understanding of schizophrenia.

Post-mortem studies have shown cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia, such as decrease in neuron size, aberrant invagination of the surface, and disruption of cortical layers suggesting a neurodevelopmental deficit in schizophrenia [4, 5]. In accordance with this postmortem evidence, MRI studies showed a reduced entorhinal volume in patients with schizophrenia [6–8]. In addition, Kuperberg et al. [9] found cortical thinning of the right medial temporal cortex in patients with chronic schizophrenia.

The entorhinal cortex is known to send major neuronal projections to the nucleus accumbens [10], which modulates dopamine release in mesolimbic areas. Animal experiments demonstrated that early neonatal lesions of the entorhinal cortex lead, after a prolonged developmental interval, to enhanced mesolimbic dopamine release and associated behavioral abnormalities such as increased locomotor activity [11, 12] in rats. In patients with schizophrenia-enhanced dopamine release in mesolimbic areas has accordingly been shown to be related to psychotic symptoms [13]. Disturbances of the entorhinal cortex might therefore constitute a relevant factor for the pathogenesis of psychotic symptoms in patients with schizophrenia. In concordance with this assumption, Prasad et al. [8] demonstrated a positive correlation between decrease in entorhinal volume and psychotic symptoms in first episode schizophrenia.

Based on these findings we hypothesized the entorhinal cortical surface area, folding index, and thickness to be smaller in patients with schizophrenia. Additionally, we expected complexity of the entorhinal cortical shape to be associated with psychotic symptoms in schizophrenia.

Therefore, we stated the following hypotheses:

1. Surface area, folding index, and cortical thickness are lower in patients with schizophrenia compared to healthy control subjects.
2. The extent of cortical folding and surface area is positively correlated with the PANSS positive subscore in schizophrenia.
3. Cortical thickness is negatively correlated with the PANSS positive subscore in schizophrenia.

In order to test our hypotheses, we performed a region of interest analysis (ROI) of the entorhinal cortex in 59 patients with schizophrenia and 59 healthy controls following computation indices for cortical surface area, folding, and thickness with an automated surface-based method.

Patients and methods

Patients

We studied 59 patients with schizophrenia and 59 healthy controls matched for age and gender. All subjects were right-handed [14]. Diagnoses were established by a clinical psychiatrist (M.R.) based on the Structured Clinical Interview for DSM-IV and were confirmed by two independent psychiatrists (R.S. and C.S.). Psychopathological ratings were performed by two experienced psychiatrists (M.R. and C.S.). All patients had no other psychiatric diagnoses. They were in remission from a psychotic episode and on stable medication, mostly with second-generation antipsychotics. They had a mean positive and negative syndrome scale (PANSS) [15] total score of 71.5 and a positive subscore of 17.3. Duration of illness showed a mean value of 3.8 years. Healthy volunteers were screened for current or previous history of psychiatric disorders as well as neurological or major medical conditions. None of the healthy subjects had first-degree relatives with a psychiatric disorder according to DSM-IV. Exclusion criteria for all participants were neurological disease or damage, medical disorders potentially influencing neurocognitive functions. All participants gave written informed consent to the study protocol approved by the Ethics Committee of the Friedrich-Schiller University. Sociodemographic and psychopathological data are given in Table 1.

MRI acquisition

We acquired high-resolution anatomical T1-weighted scans in a 1.5 T (Magnetom Vision, Siemens Medical Solutions; Germany) using a three-dimensional, rf—spoiled gradient echo sequence: 1 mm sagittal slices with TR = 15 ms, TE = 5 ms, flip angle 30°, FOV = 256, matrix = 256 × 256, number of sagittal slices = 192. All scans were inspected for motion artefacts and a neuroradiologist confirmed absence of gross pathological findings.

MR-scan processing

We used the FreeSurfer software package (version 3.3, http://surfer.nmr.harvard.edu) for processing of images [16–18]. The implemented processing stream included removal of non-brain tissue, transformation to Talairach space, segmentation of gray/white matter tissue. White and gray matter boundary was tessellated and topological defects were automatically corrected. After intensity normalization, transition of gray/white matter and pial

Table 1 Sociodemographic and clinical data

Parameter	Controls ($n = 59$)	Patients ($n = 59$)	P
M/F	39/20	39/20	
Age (years)	28.7 (8.5)	29.1 (9.4)	0.808
Education (years)	12.2 (1.4)	10.7 (1.3)	0.000
PANSS total score	n.a.	71.5 (26.0)	
PANSS positive	n.a.	17.3 (8.7)	
PANSS negative	n.a.	18.0 (7.3)	
Duration of illness (years)	n.a.	3.8 (5.67)	

PANSS Positive and negative syndrome scale

boundary was indicated by detecting the greatest shift in intensity through surface deformation. The entire cortex of each subject was then visually inspected and any inaccuracies in segmentation were manually edited. After creation of the cortical representations the cerebral cortex was parcellated into anatomical structures.

Calculation of the surface area

The surface area was calculated in mm^2 from the white surface.

Calculation of the folding index

The folding index (FI) was calculated according to Van Essen and Drury [19] as implemented in the FreeSurfer software package. The FI was calculated by integrating the product of the maximum principal curvature and the difference between maximum and minimum curvature of the white surface. The result was divided by 4 pi. A higher folding index reveals a higher folding of the cortex.

Calculation of cortical thickness

Cortical thickness was computed by finding the shortest distance between a given point on the estimated pial surface and the gray/white matter boundary and vice versa and averaging these two values. Measurements of cortical thickness were validated against manual measurements in schizophrenia [9].

ROI delineation

The parcellation of the entorhinal cortex was used as automatically implemented in the FreeSurfer Software based on the Desikan cortical parcellation scheme [20]. No manual ROI definition was needed (Fig. 1 illustrates the topography of the entorhinal cortex).

Statistical analysis

Comparison of the entorhinal cortical surface area, folding index, and thickness between patients with schizophrenia and healthy subjects

We used a GLM controlling for the effect of age to compare surface area, folding index, and thickness for each hemisphere.

F-values are based on pair-wise comparisons among the means resulting from the general linear model. *P*-values were corrected for multiple comparisons using the Bonferroni method.

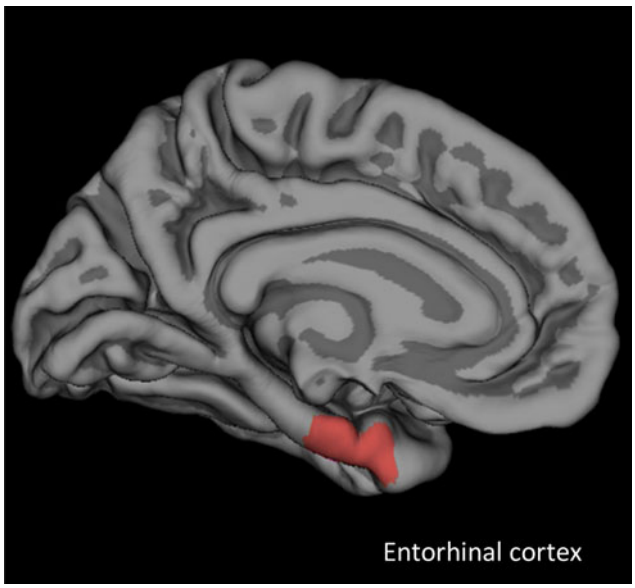

Fig. 1 Topography of the entorhinal cortex (colored in red) displaying the medial view of the left pial surface

Correlation between entorhinal surface area, folding index, cortical thickness, and severity of psychotic symptoms

In order to control for a potentially confounding effect of age we used a partial correlation to assess the relationship between the surface area, the folding index, the cortical thickness of the entorhinal cortex, and PANSS positive sum score. *P*-values for statistical correlations with the PANSS positive score and the anatomical parameters were corrected for multiple comparisons using the Bonferroni method.

Correlation between the anatomical parameters

In addition, we calculated correlations between the entorhinal cortical surface area and folding index, surface area and cortical thickness, folding index and cortical thickness for each hemisphere separately. *P*-values were corrected using the Bonferroni method.

Correlation between antipsychotic medication in chlorpromazine (CPZ) equivalents and entorhinal cortical thickness

We calculated chlorpromazine (CPZ) equivalents of the patients' concurrent antipsychotic medication [21]. We then calculated a correlation between CPZ equivalents and cortical thickness.

Results

Comparison of the entorhinal cortical surface area, folding index, and thickness between patients with schizophrenia and healthy subjects

We found a significantly ($P < 0.05$) thinner left entorhinal cortex in the patient group. No significant differences of entorhinal folding index and surface area were observed. The mean values and exact P-values are given in Table 2.

Correlation between psychopathology and entorhinal cortical shape

The left entorhinal surface area demonstrated a significant positive correlation with the severity of positive symptoms ($r = 0.35$; $P < 0.007$). In addition, the left entorhinal cortical folding index showed a significant positive correlation with severity of positive symptoms ($r = 0.36$; $P < 0.006$), whereas the correlation between right entorhinal cortical surface area and folding index with the PANSS positive score was not significant. There was no significant correlation between left ($r = -0.21$; $P < 0.116$) and right ($r = -0.01$; $P < 0.916$) cortical thickness and severity of positive symptoms.

Relation between surface area, folding, and thickness of the entorhinal cortex

Entorhinal cortical surface area showed a significant positive correlation with the folding index of the entorhinal cortex for each hemisphere (left: $r = 0.89$; $P < 0.000$, right: $r = 0.67$; $P < 0.000$). Entorhinal cortical surface demonstrated a significant inverse correlation with the entorhinal cortical thickness (left: $r = -0.36$; $P < 0.005$, right: $r = -0.48$; $P < 0.000$).

In accordance, the folding index demonstrated a strong inverse correlation with thickness of the entorhinal cortex, i.e., higher cortical folding was associated with a lower cortical thickness of the entorhinal cortex in schizophrenia (left: $r = -0.40$; $P < 0.002$, right: $r = -0.61$; $P < 0.000$).

Tables 3 and 4 summarize the results of the partial correlation. Figure 2 shows scatterplots illustrating the relation between the anatomical parameters and the PANSS positive score.

Correlation between antipsychotic medication in chlorpromazine equivalents and entorhinal cortical thickness

The mean CPZ equivalent dose of patients was 545.31 mg (SD 374.96). We found no significant correlation between left ($P = 0.724$) or right ($P = 0.362$) entorhinal cortical thickness and CPZ equivalent dose.

Discussion

Comparison of the entorhinal cortical surface area, folding index, and thickness between patients with schizophrenia and healthy subjects

To our knowledge, our study is the first ROI analysis of the entorhinal cortical shape in schizophrenia using a

Table 3 Results of partial correlation between folding and thickness parameters of the entorhinal cortex and the PANSS positive symptom score, controlling for the effect of age; P-values Bonferroni corrected

	PANSS positive score	
	r	P
Left entorhinal surface area	**0.35**	**0.007**
Right entorhinal surface area	0.05	0.735
Left entorhinal folding index	**0.36**	**0.006**
Right entorhinal folding index	0.03	0.831
Left entorhinal cortical thickness	−0.21	0.116
Right entorhinal cortical thickness	−0.01	0.916

Table 2 Comparison of the mean cortical surface area, folding index, and thickness of the entorhinal cortex between schizophrenia patients and healthy controls

Parameter	Unit	Mean (SD)		F	P
		Controls	Patients		
Left entorhinal surface area	mm^2	489.32 (98.05)	531.61 (185.90)	2.33	0.129
Right entorhinal surface area		403.63 (130.99)	383.51 (101.77)	0.86	0.357
Left entorhinal folding index	n.a.	12.02 (5.02)	12.86 (7.12)	0.52	0.472
Right entorhinal folding index		10.85 (5.49)	10.93 (4.90)	0.01	0.915
Left entorhinal cortical thickness	mm	2.93 (0.33)	2.76 (0.34)	7.76	0.006
Right entorhinal cortical thickness		2.85 (0.39)	2.82 (0.40)	0.66	0.417

F-values are based on the pairwise comparisons among the means

P-values adjusted for multiple comparisons using Bonferroni correction

Table 4 Results of partial correlation between folding and thickness parameters of the entorhinal cortex for each hemisphere, controlling for the effect of age; *P*-values Bonferroni corrected

	Left entorhinal folding index		Right entorhinal folding index	
	r	*P*	*r*	*P*
Left entorhinal surface area	0.89	0.000	n.a.	n.a.
Right entorhinal surface area	n.a.	n.a.	0.68	0.000
Left entorhinal cortical thickness	−0.40	0.002	n.a.	n.a.
Right entorhinal cortical thickness	n.a.	n.a.	−0.61	0.000

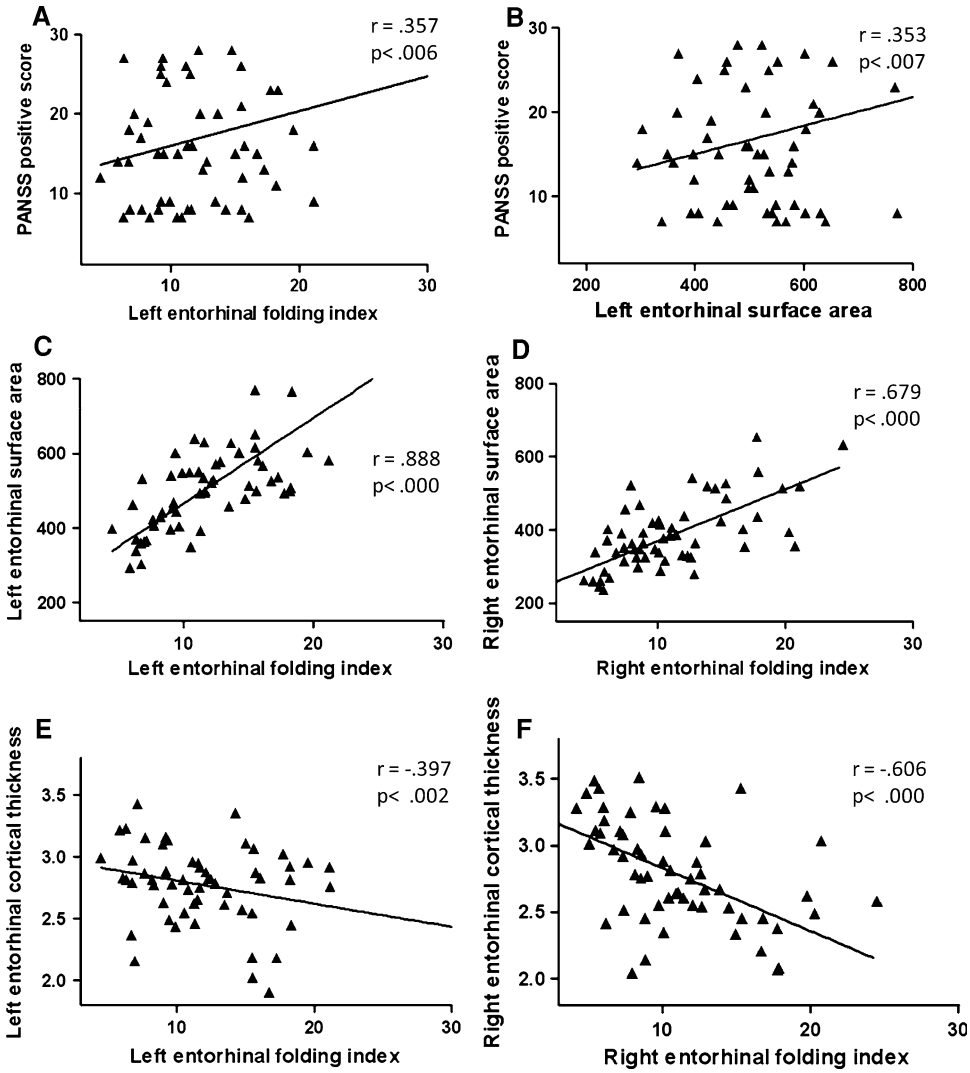

Fig. 2 Scatterplots illustrating the results of partial correlations: **a** correlation between left entorhinal cortical folding and positive sum score of the PANSS; **b** correlation between left entorhinal cortical surface area and positive sum score of the PANSS; **c** correlation between left entorhinal cortical folding and left entorhinal cortical surface area; **d** correlation between right entorhinal cortical folding and right entorhinal cortical surface area; **e** correlation between left entorhinal cortical folding and left entorhinal cortical thickness; **f** correlation between right entorhinal cortical folding and right entorhinal cortical thickness

surface-based MRI method. We observed a significantly thinner left entorhinal cortex in patients, but no differences of the cortical folding or surface area. Our finding of a thinner left entorhinal cortex is partly in line with the study of Kuperberg [9], which demonstrated a decrease in cortical thickness of the right medial temporal cortex using a vertex-wise comparison. Our result extends previous findings of decreased entorhinal volume in schizophrenia [6–8]. A decrease in cortical volume implies changes in surface area, folding, and cortical thickness [22]. However, a decrease in cortical volume might be predominantly attributed to a decrease of cortical thickness whereas cortical folding and surface area might contribute less to a decrease in cortical volume. This assumption would also be in line with to our data showing no differences in entorhinal cortical folding and

surface area. Additionally, there is some evidence that in schizophrenia the sulcal cerebral pathology is more pronounced than the gyral [23, 24]. Thus, patients and controls might be better distinguishable by sulcal rather than by gyral curvature differences. Hence, a future challenge for the investigation of entorhinal cortical folding aberrations in schizophrenia might be the specific differentiation between gyral and sulcal curvature, which cannot be measured by the folding index used in our study. Apart from that, submacrospic processes such as synaptic pruning [25], might be an additional underlying factor for aberrations in cortical folding which, however, could yet not been directly investigated with MRI techniques. There is an ongoing debate on whether alterations of cortical thickness can be taken as evidence for a neurodevelopmental origin of the disease. On the one hand, cortical thickness is affected by neurodevelopmental processes such as neuronal migration and forming of the cortical laminar structure [26]. On the other hand, cortical thickness might be more susceptible to influences of age [27] or medication than cortical folding. To date, an impact of antipsychotic medication on the cerebral cortex has been demonstrated for gray matter density in frontal, cingulate, and temporal regions [4]. An influence of antipsychotic medication on cortical thickness has not been proven [28]. Hence, we additionally analyzed our data to explore a potential impact of cortical thickness and antipsychotic medication. We found no correlation between entorhinal cortical thickness and antipsychotic medication, which is in line with the study of Nesvag [29]. Thus, it seems to be unlikely that the difference in left entorhinal cortical thickness between patients and healthy controls in our study is based on antipsychotic medication effects.

Relations between the entorhinal cortical surface area, folding index, and positive symptoms in schizophrenia

Consistent with our a priori hypothesis, we found that the severity of psychotic symptoms was associated with a larger surface area and a higher cortical folding of the left entorhinal cortex in patients with schizophrenia. Postmortem studies of the entorhinal cortex show that a neuronal migrational deficit is present in patients with schizophrenia [5, 30–34]. Neuronal migration and the formation of cortical folding are processes of brain maturation. These processes influence each other. Hence, cortical folding can be considered as a marker of integer brain development [26, 27]. Disturbance of neuronal migration has not been explored in vivo yet, but modern surface-based imaging techniques offer the possibility to investigate cortical folding. Our findings might therefore indicate that a disturbed folding process of the entorhinal cortex might be one of the neuroanatomical bases for the development of psychotic symptoms in schizophrenia. In addition, according to mechanical models of cortical shaping [35], neuronal migrational deficits could come along with a disturbed cortical folding of the entorhinal cortex [31]. A disturbed migration of entorhinal neurons might indirectly reflect one underlying process leading to psychotic symptoms in schizophrenia. A stronger local cortical folding accompanies a larger local surface area. Thus, our findings indicating that the surface area of the entorhinal cortex is also positively correlated with the severity of psychotic symptoms are consistent with the association between entorhinal folding and psychotic symptoms.

In addition, our data are also in accordance with the results of animal experiments on rats lesioned in the entorhinal cortex, which may lead to a model of the pathogenesis of psychotic symptoms in schizophrenia [11, 12]. Moreover, the fact that we found a positive correlation between these anatomical parameters and the severity of psychotic symptoms in the left hemisphere, is consistent with results showing that alterations of the entorhinal cortex might be more pronounced in the left hemisphere [8].

Thus, our data reveal new in vivo evidence for the involvement of the entorhinal cortex in the pathogenesis of psychotic symptoms in schizophrenia.

Relation between cortical thickness of the entorhinal cortex and positive symptoms in schizophrenia

At first glance it seems to be astonishing that we found no correlation between the severity of psychotic symptoms and entorhinal cortical thickness. But regarding results of postmortem studies of the entorhinal cortex in patients with schizophrenia, this finding is plausible.

Postmortem studies found an aberrant invagination of the entorhinal cortical surface, a disruption of cortical layers, a heterotopic displacement of neurons, and a paucity of neurons in superficial layers [5]. Furthermore, a quantitative assessment of neuron clusters indicated that these clusters were positioned closer to the gray–white matter junction of the entorhinal cortex in patients with schizophrenia compared to healthy controls [31]. This displacement of neurons might be functionally relevant. It is, however, not necessarily detectable through the measurement of cortical thickness, but might get unveiled in the form of an aberrant cortical folding. This assumption is supported by our data showing no significant correlation of entorhinal cortical thickness and severity of psychotic symptoms. Hence, cortical folding might be a more relevant cortical parameter than cortical thickness to determine the psychopathology in patients with schizophrenia.

Entorhinal cortical shape parameters and mechanical models of brain development

Our finding that cortical thickness is inversely correlated with the degree of cortical folding in schizophrenia also corresponds to mechanical models of cortical shaping [26, 27, 36]. Forces generated by cortical folding influence laminar morphology and have an impact on cellular migration during cortical development. These models suggest that, due to these centripetal forces generated by corticocortical connections in brain maturation, higher cortical folding is associated with a reduced cortical thickness. According to these mechanic models, our analyses illustrate that the cortical folding of the entorhinal cortex is inversely correlated with cortical thickness.

Entorhinal fiber tracts and a potential impact on psychopathology

Kalus et al. [37] demonstrated altered structural integrity of entorhinal fiber tracts which supply the limbic system with neuronal input, so that also white matter abnormalities of the entorhinal region might have an impact on psychopathology in schizophrenia. Therefore, in order to further specify the role of the entorhinal cortex in schizophrenia combining different MRI methods seems to be a promising approach for future studies.

In conclusion, we present new evidence for the involvement of the entorhinal cortex in the pathogenesis of psychotic symptoms in schizophrenia. As cortical folding is a stable neuroanatomical parameter terminated in early neonatal stages, our data give reason to assume that the vulnerability to develop psychotic symptoms might be manifest at an early level of brain maturation. Hence, our finding gives support to results which suggested a neurodevelopmental pathogenesis of schizophrenia.

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