

## Review Article

# Neurodevelopment Hypothesis of Schizophrenia and the Structural Neuroimaging as a Tool to prove it

Andriana Kakanakova\*

Department of Psychiatry and Psychology, Medical University, Plovdiv, 15 A, V. Aprilov. Blvd, Plovdiv

### \*Corresponding Author

Dr. Andriana Kakanakova  
Department of Psychiatry and Psychology,  
Medical University, Plovdiv, 15 A, V. Aprilov. Blvd,  
Plovdiv  
E-mail: [andriana\\_kakanakova@hotmail.com](mailto:andriana_kakanakova@hotmail.com)

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### Abstract

According to the neurodevelopment hypothesis of schizophrenia it is a disorder due to brain damaging during the intrauterine or early childhood years, manifesting decades later symptomatically. In a metaanalysis in 2001, 193 magnetic resonance imaging (MRI) structural studies have been reviewed. The data confirmed earlier findings by computer tomography (CT) studies – consistent enlargement of the lateral and third ventricles and decreased volume of the temporal lobe. Decreased volume of the whole brain, ventricular dilatation, widening of the brain sulci are features defining brain atrophy. The most common CT markers of defining the brain atrophy are: 1) Internal cerebrospinal fluid amplitudes: Frontal horns index (FHI); Huckmann's number (HZ); Cella media index (CMI); III and IV ventricle amplitudes. 2) External cerebrospinal fluid amplitudes: Cisternae insulares, Frontal interhaemispheric sulcus, Number of the sulci, Sulci width. 3) Temporal lobe amplitude. The new directions of studying the structural anomalies of the schizophrenic brain lean towards studying more homogenic groups of patients, linking the changes to actual stages of the disorder, comparing structural with functional changes.

## 1. Background

According to the neurodevelopment hypothesis of schizophrenia it is a disorder due to brain damaging during the intrauterine or early childhood years, manifesting decades later symptomatically.

## 2. Risk factors in developing Schizophrenia

According to the latest data available [1], neurodevelopment hypothesis is still valid. It implies the acting of different pathological agents during the intrauterine development.

### 2.1 Prenatal and perinatal factors

According to different studies, maternal exposure to influenza, malnutrition, Rhesus incompatibility, diabetes during the pregnancy, ablation of the placenta, gestational bleeding, can lead to neuroembriological infractions [2].

There are different directions of studying supporting this hypothesis [3] – epidemiological data on the impact of infectious agents and stress during pregnancy [4], perinatal complications [5], preceding behavioral deviations and neuromotor deficits [2] absence of postmortem gliosis [6].

The offspring of women with high levels of immunoglobulins (IgG and IgM) and Herpes simplex antibodies during pregnancy show increased probability in developing Schizophrenia and other psychiatric disorders in adulthood [7].

Other possible risks are malnutrition of the pregnant and stress during pregnancy (i.e. war, floods, etc). Increased cortisol levels are likely in Schizophrenic patients as a response to different agents – physical and psychological stress, which can result in impaired neurodevelopment [8].

### 2.2 Viral infections

We can assume that 5-10% of cumulative risk of developing Schizophrenia is due to influenza infection during pregnancy [9, 10], based on studies on the prevalence of the disorder in children (especially

girls) born by women experienced flu infection during second trimester. Similar study in England and Wales, found that Schizophrenic patients, born shortly after the 1957 influenza epidemic has been 88% more than the number of patients two years before and after the epidemic. It is presumed that influenza virus affects embryogenesis of the brain directly- affecting cell migration and indirectly by stimulating immune reactions causing dysplasia [11].

Watson et al report a connection between yearly occurrence of schizophrenic births and preceding diphtheria and varicella, pneumonia and influenza morbidity in Minnesota in 1916-1958. Warner and Girolamo found relation between the occurrence of schizophrenic births and varicella but not in case of influenza [12].

There is a seasonal pattern in the birth of schizophrenic patients which supports the hypothesis of the acting of a viral agent. Offspring with risk of developing Schizophrenia (born by mothers with Schizophrenia) that do develop the disorder are more likely born in the winter and raised in urban environment, i.e. favorable of viral infections, compared to ones who does not develop the disorder [11]. A study among Swedish families found significantly increased risk of developing Schizophrenia in case of 3-4 years old siblings in the family who appear to be the main carrier of viral infections in the household [12].

### 2.3 Season of birth

The yearly graph of birth among schizophrenic patients shows clear peak in the winter and early spring period. Patients who have been born in these months that develop Schizophrenia later in life are 5-10% more [13,14]. Such clear pattern has not been found in other psychiatric disorders which strengthen the hypothesis that this phenomenon is relatively typical for this disorder. The presence of neuroontogenetic effect on the occurrence of winter births is confirmed by neuroimaging as well. Ventricular dilatation has been found in patients with schizophrenia, born in the months December to April. It is found more often in the sporadic Schizophrenia cases and in patients with no family history for Schizophrenia [15] or has been born and raised in urban

environment [8], where there is higher level of population, contagiousness and morbidity.

#### 2.4 Social risk factors

There is strong evidence that social risk factors contribute to the development of Schizophrenia.

1. Adverse upbringing
2. Urban upbringing
3. Social isolation
4. Migration
5. Substance abuse
6. Incidents and stress

Animal models show that the exposure to ontogenetic agents causes vulnerability to social stress[16]. Same has been postulated about humans [17] and can give an explanation why ill environment can bring harm to ontogenetic impaired individuals. Stress does not appear to be so harmful to aggressive persons, i.e. aggression compensates in its way the destructive stress effect. Chronic exposure to tobacco smoke induces oxidative stress in cells and causes biochemical imbalance [18].

#### 3. Biomarkers (bm) and schizophrenia

Biomarker (BM) appears to be a measurable sign of a disease that may be casual[19]. BM are of great interest in all fields and areas in medicine, especially after revealing the human genome[20]. There is a number of forensic findings studies and neuroimaging data as well about the presence of structural aberrations in schizophrenia patients as decreased volume of the brain (due to whole brain cortical atrophy); ventricular volume (third and lateral ventricular volume increased) [9], presumably due to subject changes in the paraventricular basal ganglia (enlarged neostriatum)[21]; decreased volume of the temporal area[22]; and prefrontal cortex (PFC) – dorsolateral PFC in particular [23]; unspecific changes in the cerebellum vermix.

#### 4. Structural neuroimaging – Computer Tomography (CT), Magnetic Resonance IMaging (MRI)

In a metaanalysis made in 2001, 193 MRI structural studies have been reviewed [24].

The main issues were are there really structural anomalies in the schizophrenic brain and if so, is there a specific pattern and specific brain areas affected. The other important question was if these findings confirm the neurodevelopment, otherwise called neuroontogenetic hypothesis of schizophrenia, or the neurodegenerative hypothesis. The data confirmed earlier findings by CT studies – consistent enlargement of the lateral and third ventricles and decreased volume of the temporal lobe [23].

80 % of the studies show enlarged lateral ventricles, compared to controls, although this changes are unspecific. Another frequent finding is damage of the temporal lobe - 74 % of 49 studies show decreased volume of the amygdala, hippocampus, parahippocampal structures and neocortical structures as STG- superior temporal gyrus. Third come consistent enlargement of the third ventricle in 73 % of 33 studies, 59 % of 50 studies show decreased volume of the frontal area, 68 % of 25 studies- basal ganglia anomalies, 42 % of 12- decreased volume of the thalamus, and 31 % of 13 – decreased volume of the cerebellum[1].

There is some electroencephalography changes present in schizophrenia patients as decreased alfa, increased teta and delta activity, lower seizure threshold. There is evidence of higher auditory sensitivity, especially to background buzz, which may cause the auditory hallucinations. Schizophreniform disorder is frequent in patients with partial temporal epilepsy [1].

The patch-clamp is a sophisticated tool to investigate the electrophysiological activity at the single cell and even on ion-channel

level can be used for a systematic study of the ion-transport across the cell membrane [25].

#### 5. Pathological CT findings and symptoms of brain atrophy

Since the introducing of the CT scanning in the mid 70s of 20<sup>th</sup> century, the statement of Becker: „ CT is the best method of proving brain atrophy” is still valid.

Decreased volume of the whole brain, ventricular dilatation, widening of the brain sulci are features defining brain atrophy.

The most common CT markers of defining the brain atrophy are:

**1. Internal cerebrospinal fluid amplitudes:** FHI – frontal horns index; HZ – Huckmann’s number; CMI – Cella media index; III and IV ventricle amplitudes.

**2. External cerebrospinal fluid amplitudes:** Cizternae insulares, Frontal interhaemispheric sulcus, Number of the sulci, Sulci width

**3. Temporal lobe amplitude[26]**

Existent CT findings in schizophrenia due to brain atrophy are confirmed in a pilot study in Bulgaria on 22 schizophrenia patients (according to DSM-IV criteria), compared to 27 healthy controls, homogenous by ethnicity (Bulgarian), native CT scan has been held, +15 to -20 degrees to orbitomeatal line cuts. Cortical atrophy has been rated according to Meese and Groome criteria. There is consistent enlargement of the lateral ventricles in schizophrenia patients compared to healthy controls and enlargement of the lateral and convex sulci. These findings suggest pathological process acting before completion of brain development [3].

#### 6. Conclusions

The new directions of studying the structural anomalies of the schizophrenic brain lean towards studying more homogenic groups of patients, linking the changes to actual stages of the disorder, comparing structural with functional changes [1].

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