

## **THEORY ON THE EMBRYO-VASCULAR ETIOLOGY OF THE SCHIZOPHRENIA**

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### **Summary**

The embryo-vascular theory starts from the made observations from many researchers on the alterations of volume of any cerebral districts. These reductions of volume concern organs like amygdala, thalamus and hippocampus particularly, that, according to this theory, are the greater responsible of the alterations of cerebral operation that characterize the syndrome schizophrenic. This theory hypothesizes that the alterations subcortical are of origin embryologic and that those cortical are "secondary" to the inefficient functioning of the districts subcortical.

### **Introduction**

An of the more accredited hypotheses on the etiology of the schizophrenia is that this illness derives from anomalies of the cerebral development. Already in the 1990 Roberts affirmed that the anomalies of cingulum, hippocampus and amygdala was not degenerative, on the contrary tied to an anomalous development of the brain, while numerous researchers directed the attention to the processes of selection and/ or migration of the cells in the first phases of the development of the fetus. The hypothesis of a cause embryonic part also from clinical evidences according to the schizophrenia is frequent in those subjects with a fetal history of viral infections, processes autoimmunic and other maternal pathologies (1). Besides Lieberman report a study in which it is observed that the 2/ 3 of the patient schizophrenic had histories of obstetric complications (2). The system nervous central appear to the beginning of the third week of pregnancy from the ectodermic membrane disguised as naural plaque. To the fifth week the part cephalic of the plaque contains three expansions: the prosencephalon, the mesencephalon and the rhombencephalon (3). The diencephalon starts from the prosencephalon, from a single layer of ependymal cells dressed from vascular mesenchyma (choroid plexus of the III° ventricle). The neurons of the future telencephalon, during the development, move themselves in direction rostral and dorsal, turn around the diencephalon, following a way to form of C that goes toward the anterior pole of the temporal lobe. The cerebral organs interested from this complex migration are: to) the hippocampus that in the rotation to C toward the temporal lobe gives birth to the fornix, b) the amygdala that, like its wake, carries to the formation of the terminal stripe c) the lateral ventricles, d) the caudate nucleus.

According to Bonavita also nucleuses of the base and thalamus has the cellular migration to C (4). The cellular migration, that is longest and tortuous undertaken from the cerebral cells, accompanied from the arteries and veins choroid, that do the same journey. This process begins about at seventh week (5). In this rotation the corpus callosum presents a later development regards the other mentioned districts, appearing about the tenth week and rotating to C on the tectorial lamina of the diencephalon. In accordance with authoritative texts the period of pregnancy that is mostly sensitive to the pathogenic noxa is that of the III week ( gastrulation) , where even an abuses alcohol could produce notable consequences on the fetus, while are many the drugs that could alter the process of migration, between these the vitamin A , the talidomide, the warfarin, the aminopterin and the antiphospholipids, (3-6). The disorders of the migration are instead more frequent between 18° and the 24° week and the causes mostly recognized are: a) intrinsic anomalies of the neurons and/ or of the glia, b) anomalies of factors of induction and suppression of the cellular migration, c) traumas, vascular disorders, infections and drugs (4). Between the pathogenic agents more recognized are indicated : cytomegalovirus, herpes simplex, hepatitis, poliovirus , echovirus, coxsackie virus, virus of influenza and toxoplasmosis. In this regard Torrey of the Medical Research Institute of Maryland and Joanne Webster of the Imperial College of London would have discovered that the schizophrenics patients have a triple concentration of antibodies antitoxoplasmosis as regards the general population.

In the human brain the cerebral vascularization is granted by the arteries that depart from the polygon of Willis: the arteries cerebral anterior, cerebral medium and back, joined between them from the communicating anterior and back. Very are the anomalies in the polygon of Willis: often the communicating back are atrophic (in the 60% of the cases) (7), and sometimes are atrophic also the communicating anterior. Between the other anomalies we discover the hypoplasia of the communicating anterior, the hypoplasia of the initial tract of the cerebral anterior artery or agenesis of the same, and the origin of the cerebral back artery that leave from the artery inside carotid (7). For our treatment ,we will consider the anterior choroid arteries, choroid back and communicating back . The anterior choroid arteries supply the part mediate of the pallidum , the hippocampus, the amygdala, the lateral geniculate body of the thalamus, the back arm of the inside capsule, the lateral ventricles and the tail of the caudate nucleus (8). The communicating back arteries supply the optic chiasm, the hippocampus, the cerebral peduncle, the thalamus and the back arm of the internal capsule. Finally the arteries back choroid supply the corpus striatum and the thalamus (7). If we go to assemble in groups, making correspond to each cerebral organ the group of arteries that they supply it, we will have that the amygdala is supplied from the anterior choroid artery, the hippocampus from the choroids anterior artery and communicating back , while the thalamus is served from the anterior choroid, communicating back artery, from the artery cerebral back and from the back choroid.

Innumerable jobs, effected in the last decades, signal the reductions of volume of the whole cerebral mass (9-10-11), of the zones medial temporal (35-36-37-38)of the amygdala and of the hippocampus (12-13-39), of the medial temporal lobe, superior temporal gyrus and hippocampus (14-15). Many other studies concern the reduction of volume of the amygdala (16-17-18-19-20), of the thalamus (21-22-23), particularly of the medial dorsal nucleus. And likewise numerous are the jobs that describe reductions of volume of the hippocampus, examined separately (24-25-19-20).

They have reported, besides, recent jobs that have put relationship the reductions of volume of any cerebral districts and the complications during the pregnancy (26) in hold. Innumerable studies also reported the amplification of the I° and II° ventricles and alterations of the terminal stria, that, we remember, is produced like wake of the migration to C of the amygdala. Very more recent studies have underlined an atrophy of the anterior part of the cingulated gyrus (27-28) also.

If we take a step backward and we go to examine the cellular migration and the organs that move themselves according to a journey to C, very complex and along, we can share between their organs like the thalamus, the amygdala, the stria terminal, the hippocampus, the temporal lobe and arteries like the anterior and back choroid. It is a strange coincidence to discover that these structures are shared from a tortuous embryonic migration, happened in the same week of pregnancy, in a period that results be most sensitive to the physical, infectious and external insults of varied nature. And it is likewise strange that amygdala, thalamus and hippocampus are reported from years like hypoplastic and that they are supplied almost exclusively from the choroid arteries. It is plausible that a noxa pathogenic that intervenes in the first weeks could alter the migration of the cells of these structures determining a hypoplasia of the involved arteries and, probably, a reduction of number of cells proliferated and/or migrated in the mentioned organs. It would not be an inflammatory chronic process, (in fact in the brain of the schizophrenic patient there is not gliosis, index of inflammation), but an insult intervened and finished in a specific period of pregnancy; after all also Weinberger already in the 2002 supported that the neuropathologic changes of the schizophrenia was not progressive. In effects till now are examined always the big vases (40-41-42) of the brain of the schizophrenic, when instead it could hypothesized that the problem resides in the vases of small and middle caliber like the anterior and back choroid arteries and the communicating back. We don't forget that the cerebral arteries are of type "terminal", in fact they supply territories that only to their peripheries could be served from collateral vases. The literature, besides, is full of anomalies embryonic of the vases that causes the reduction of the vascular lumen, like the fibermuscular dysplasia, the illness of Moyamoya, the aortic coarctation in which the vase is narrow for anomaly of the middle tunic, with intimal proliferation. Accepting the hypothesis that the hypoperfusion of these cerebral relais, causes the hypotrophy of themselves, we could identify the primum movens of the etiology of the schizophrenia in a cause embryologic and vascular together.

But what is the pathogenic mechanism? The amygdala, the thalamus and the hippocampus is three fundamental relais for our brain; they act from filter for all the information that arrive from the inside and from the outside of our body. All the systems sensory arrives at the lateral basal nucleuses of the amygdala and to the nucleuses of the thalamus, particularly to the dorsomedial nucleus, to be then sorted to the varied zones cortical. But these three organs are not only a point of receipt and clearing of the stimuli, in the sense that they don't receive stimulants from the peripheries to send them passively to the cortex, they act probably from "filters" avoiding that useless, repetitive or irrelevant stimulants for our life, could overload the cortex. In effects these intermediary stations sort only that it is useful to our existence. When we look at the external world and listen to the its sounds, our brain doesn't set attention to all the informations, it doesn't transmit all to level of conscience, until to the cortex. All of what we see or we hear, stop in intermediary stations, like amygdala and thalamus.

But if these relays are hypotrophic for the vascular and embryologic problems above exposed, we are able to well understand like their function of filter fails: this means that many or all the information (useful and useless) inexorably arrives at to the cortex. We imagine, for an instant, a cortex "bombed" from all a set of informations, many of which useless: this would mean to flood the structures cortical, with an overload that any would weaken the functional abilities in the course of the years. In effects the associative functions and of elaboration of the cortex would be inexorably weaken and compromised, "releasing" ,with the time, the structures subcortical from any "supervision cortical" (to see the theory "The speculate brain" of the same author published to August 2009 on Pharmacologyonline. But how each organ insufficient , also the brain apparent his deficit in particular conditions: when it is under effort. This would leave that the interpretative anomalies of the reality and the behavioural alterations could develop above all in a phase of the life, like the adolescence, where the close of the cerebral maturation should correspond to a bigger request of cerebral activity, both from a point of view rational and emotional; in fact the myelinization of the white cerebral substance continues and reaches the peak, not at random, in the second decade (29). Under this "effort" the brain would begin to vacillate, for an alteration of filter of the zones subcortical and a hyperactivity of the afferents to the same zones cortical. It is this the reason for which the schizophrenic symptomatology has a beginning that happen in the period of the adolescence, staying a pathology asymptomatic for many years. The clear symptoms happens subsequently, but the strangeness behavioural , the isolation and the others vanished prodromic symptoms happen much sooner. This concept ties itself to the made affirmations in a symposium to San Diego in the 2009" New perspectives on progression of brain abnormalities in psychosis" according to which the lesions that are in the schizophrenics patients are physiological after the 35 years of age, but they in the schizophrenia are already present from the 25 years. This would testify that it is a brain in which any districts deteriorated themselves ahead of time . Many studies put in evidence the volumetric and of consistence alterations of the grey and white substance of many zones cortical like the temporal superior lobe , inferior frontal , cingulum and fusiform gyrus (30) and decrement of the density of the grey temporal, frontal and thalamic substance (31). If we depart from the presupposition that the theory is valid, and that the responsables of the "imbalance of strengths" between cortex and subcortex are the subcortical zones , we could hypothesize that the other structural alterations and/ or volumetric of other organs (cortex prefrontal, gyrus of the cyngulus, cortex temporal etc) they are only one consequence of an overload of input that continues in the years; like if it is about a slow corrosion of the cortical structures , that in the course of the years remain "victims" of the hyperactivity of the subcortical zones. In fact many studies have underlined like the alterations of any cerebral districts are late regards to the course of the illness: the frontal horn widened in the chronic patients (Bilder 94), the head of the caudate nucleus is hypertrophic , perhaps for the chronic use of drugs (Chakos 94)(34), the volume of the temporal lobe decreased is decreased in the chronic patients (32), structural anomalies of the cortex prefrontal and temporal are fruit of the chronic use of drugs (33).

This job represents a stimulus to go beyond the conventional interpretation of the schizophrenics symptoms; until the end of the 900 the shortage of examinations and instrumental equipments induced the researchers to imagine the mechanisms of the schizophrenia departing from the effect of the drugs and of their action on the neurotransmitterial circuits. But the action of the neuroleptics that tie the receptors D2 could be explained also hypothesizing that the block of the dopaminergic tracts that goes from the brainstem to the subcortex, determines a reduction of the hyperafflux of

input from the peripherics toward the cortex (spending for the subcortex), reducing the congestion of afferent messages accordingly and allowing to the cortex of resume work (to more bearable regimes). Many new techniques of neuroimaging and of laboratory allow today to may examine our brain with better precision, allowing to acquire data that were unthinkable until to any years ago. To this point it would be desirable verify this hypothesis with instrumental examinations that evaluate the cerebral circulation in the brain of the schizophrenics, setting particular attention to the vases of small and middle caliber, noting of the varied phases of the illness in the course of the years. If the theory is validated, this would open new sceneries for the cares and the prevention of the schizophrenia, orient the interventions in the primordial phases of the process pathologic, focusing the attention on the life embryologic of the individual. This job doesn't have the pretension of exhaustive being, but it wants to represent a possible mechanism etiological of the schizophrenia, a stimulating point of view for how many want to deepen the study of this illness.

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