

# Neurodevelopment and schizophrenia: data on minor physical anomalies and structural brain imaging

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The neurodevelopmental hypothesis of schizophrenia suggests that subtle anomalous brain development occurs in utero which reveals itself symptomatically, years later, as the heterogeneous symptoms of schizophrenia. This paper shortly reviews data on the presence of minor physical anomalies in those affected by schizophrenia and also summarizes a few results from structural brain imaging studies, which promote the neurodevelopmental hypothesis of the disease.

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## NEURODEVELOPMENT AND SCHIZOPHRENIA

Most recently in a meta-analysis of structural magnetic resonance imaging studies Olabi and colleagues (Olabi et al., 2011) state that the dichotomy of the neurodevelopmental and neurodegenerative hypothesis is artificial, as the pathophysiology of schizophrenia may contain both processes (Balla and Frecska, 2011). A similar view was supported much earlier by Woods (Woods, 1998). Although findings suggest that schizophrenia is associated with progressive structural brain abnormalities (Olabi et al., 2011), it is also evident that the neurodevelopmental model remains the central hypothesis of the disease (Keshavan et al., 2008). The neurodevelopmental hypothesis of schizophrenia suggests that subtle anomalous brain development occurs in utero which reveals itself symptomatically, years later, as the heterogeneous symptoms of schizophrenia (Weinberger, 1995). Several diverse lines of evidence support this model (Weinberg et al., 2007) including epidemiological data (e.g. in utero disease and stress exposure, reviewed in (Cannon et al., 2004), the presence of obstetric complications (McNeil et al., 2000; Cannon et al., 2002), the presence of premorbid behavioral and neuromotor deficits (Walker and Lewine, 1990) and the absence of gliosis at postmortem (Falkai et al., 1999). In this paper I will shortly review data on the presence of minor physical anomalies (MPAs) in those affected by schizophrenia and I will also summarize a few results from structural brain imaging studies, which promote the neurodevelopmental hypothesis of the disease.

## MINOR PHYSICAL ANOMALIES IN SCHIZOPHRENIA

Minor physical anomalies are mild, clinically and cosmetically insignificant errors of morphogenesis which have a prenatal origin and may bear major informational value for diagnostic and prognostic purposes (Tenyi et al., 2009). The presence of MPAs is a sensitive physical indicator of embryonic development (Trixler et al., 2001). They are value to clinical morphologists as they serve as indicators of altered morphogenesis that occurred early in gestation. Since both the central nervous system and the skin are derived from the same ectodermal tissue in utero, MPAs may be external markers of abnormal brain development (Trixler et al., 1997; Trixler et al., 2001; Tenyi et al., 2009; Méhes, 1985).

Several studies have shown an excess of MPAs in patients with schizophrenia (Gualtieri et al., 1982; Green et al., 1989; O'Callaghan et al., 1991; Lohr and Flynn, 1993; McGrath et al., 1995; Lane et al., 1997; Trixler et al., 1997; Trixler et al., 2001; Ismail et al., 1998; Weinberg et al., 2007). In the vast majority of studies, the Waldrop scale (or some variant thereof) has been used to assess MPAs in schizophrenia. As we have summarized before (Tenyi et al., 2009; Trixler and Tenyi, 2000; Trixler et al., 1997) differences between studies may be associated, partly, with the problems in the use of the Waldrop scale and connecting to this, we have introduced a new scale, the Méhes scale, for the assessment of MPAs in patients with different neuropsychiatric diseases (Trixler et al., 1997; Trixler

et al., 2001; Tenyi et al., 2009; Csabi et al., 2008). The Waldrop scale contains only 18 MPAs (Waldrop és Goering, 1971), while in the pediatric literature more than 50 MPAs have been listed (Mehes, 1985). In the Méhes scale, which is used by our research group, we assess 57 minor signs. The bigger problem with the Waldrop scale that it does not differentiate the two different types of minor physical anomalies (Trixler and Tenyi, 2000), so summarized results with the scale are not able to give information on the timing of the supposed genetic or environmental insults, which possibly result abnormal brain development. While minor malformations are always abnormal, they are qualitative defects of embryogenesis and arise during organogenesis. In contrast, phenogenetic variants are quantitative defects of final morphogenesis and arise after organogenesis, and they are exact equivalents of normal anthropometric variants (Tenyi et al., 2009; Opitz, 1985; Mehes, 1985). By the use of the Mehes scale we have found that patients with schizophrenia had significantly higher rates of three minor malformations (furrowed tongue, haemangioma and multiple buccal frenula) comparing with matched patients with the diagnosis of alcohol dependence (Trixler et al., 1997). Studying another sample, we have reported, that patients with schizophrenia compared to normal controls had significantly higher rates of three minor malformations (furrowed tongue, flat occiput, primitive shape of ears) and they also had a significantly higher rate of one minor malformation (primitive shape of ears) as compared to patients with bipolar affective disorder (Trixler et al., 2001). Our findings indicated that specific anomalies of the mouth and head may have more relevance to the hypothetical neurodevelopmental failure than does the cumulative prevalence of MPAs (Trixler et al., 2001). Other studies also confirmed a higher frequency of abnormalities of the mouth and the head (Green et al., 1989; O'Callaghan et al., 1991; Hata et al., 2003; Gourion et al., 2004).

In a recent meta-analysis of 13 studies using the Waldrop scale, it was found, that the pooled effect size for the total MPA scores was high ( $p=0.001$ ), indicating significantly more overall MPAs in schizophrenic individuals (Weinberg et al., 2007). In this meta-analysis results suggest a lack of regional specificity for MPAs (included in the Waldrop scale) in schizophrenia. Further studies using detailed scales and meta-analysis of these should clarify the predictive value of MPAs in high-risk individuals for schizophrenia.

## STRUCTURAL BRAIN IMAGING AND THE NEURODEVELOPMENTAL HYPOTHESIS

A robust support of the neurodevelopmental hypothesis of schizophrenia appeared in the 1970s and early 1980s, when noninvasive structural brain imaging techniques began to have an impact on schizophrenia research. In 1976 Eve Johnstone and colleagues published the first computer-assisted tomography study of schizophrenia, which have showed enlarged lateral ventricles in schizophrenia. This first study led to many similar CT studies, with 75 percent of CT studies showing enlarged lateral ventricles in schizophrenia, compared with healthy controls (Shenton and Kubicki, 2009). The limitations of CT were considerable in that it showed little in the way of anatomical detail within brain structure.

The emergence of magnetic resonance imaging (MRI) made it possible to differentiate the white matter from the gray matter within the brain. In the late 1980s the first wave of MRI studies replicated the findings already established with CT: that there were increases in the volume of cerebrospinal fluid, while the second wave of MRI studies reported reduction in gray matter volume in medial temporal structures including hippocampus-amygdala and parahippocampal gyrus (Lewis, 1997). A third wave of MRI studies extended the area of interest from the temporal lobe to the gray matter in general. The first two studies reported a generalized reduction in cortical gray matter volume over the brain of between 4 and 18% in schizophrenia compared with control subjects (Zipursky et al., 1992; Harvey et al., 1993). Reviewing data in 1997 Lewis suggested, that there was a 5-8% global reduction in cortical gray matter in schizophrenia based on the results of several studies which have looked and failed to find a correlation between length of illness and the degree of volumetric reduction, which suggests that this change is neurodevelopmental rather than degenerative in pathology (Lewis, 1997).

In a 2001 review, Shenton and colleagues examined 1993 peer-reviewed MRI structural studies. In 55 lateral ventricle MR studies reviewed, 80% reported enlarged lateral ventricles in patients with schizophrenia compared with controls. 74% of 49 studies showed medial temporal reduction of structures that included the amygdala, hippocampus, parahippocampal and neocortical temporal regions. In 33 third ventricle studies, 73% showed enlarged third ventricle. 60% of 15 parietal lobe studies showed volume reduction in schizophrenia, while 59% of 50 frontal lobe studies

showed volume reduction in schizophrenia. It is very important from our point of view here, that 92% of 12 studies of cavum septum pellucidum showed enlarged cavum, indicating a neurodevelopmental background of schizophrenia (Shenton et al., 2001). This review and also most recently Shenton and Kubicki (Shenton and Kubicki, 2009) state, that the “pattern and number of abnormalities are consistent with a disturbance of connectivity within and between brain regions, most likely of neurodevelopmental origin, although there is some suggestion that some regions such as superior temporal gyrus may show progression in volume reduction even early in the course of the illness”.

A very important line of research is the MRI studies of first-episode patients. These studies beside other important of questions can answer two fundamentals as (1): are brain abnormalities present at the first onset of the illness, which would mean that there is a strong neurodevelopmental component in the background of the disease, (2) and if present, are these abnormalities static or they progress? In the last years, a large number of MRI studies have examined different cortical and subcortical regions in first-episode schizophrenic patients. Most of the studies have demonstrated a similar pattern of brain abnormalities to that reported in samples of chronic patients, while a few other studies reported nonsignificant changes of different brain structures (Vita et al., 2006). To clarify the field, Vita and colleagues (Vita et al., 2006) performed a systematic search for MRI studies that reported quantitative measurements of volumes of brain regions in first-episode schizophrenic patients and in healthy controls. 21 studies were identified and the results show lateral and third ventricular volume increase and a volume reduction of the whole brain and the hippocampus. This meta-analysis did not confirm a significant reduction of temporal lobe and amygdala volumes in first-episode patients, which can mean that some known brain abnormalities in schizophrenia are not present at the first onset of the illness, which supports the hypothesis of different patterns of involvement of various cerebral structures over the time of the disease (Vita et al., 2006).

The combination of methods of structural brain imaging (for example MRI with diffusion tensor imaging) and also with fMRI may clear up alterations in the brain of patients with schizophrenia, that subserve networks such as language, emotion, attention or theory of mind (Shenton and Kubicki, 2009). In a voxel-based morphometric study, our group has found that poor theory of mind performance correlated

with gray matter reduction in the left orbitofrontal cortex and the right temporal pole in the early phase of schizophrenia (Herold et al., 2009).

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## Az idegfejlődés és a szkizofrénia: minor fizikális anomáliák és strukturális agyi képzőanyagok

A szkizofrénia idegfejlődési hipotézise szerint egy prenatálisan létrejött agyfejlődési zavar manifesztálódik évekkel később a betegség tünetében. Ebben a közleményben összefoglalást nyújtok a minor fizikális anomáliákkal és a strukturális agyi képzőanyagok eljárásokkal kapcsolatos kutatásokról.

**Kulcsszavak:** idegfejlődés, minor fizikális anomáliák, strukturális agyi képzőanyagok, szkizofrénia