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Iris structure and minor physical anomalies in schizophrenia

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ABSTRACT

This study compared five human iris characteristics and minor physical anomalies (MPAs) between patients with schizophrenia (n = 32) and controls (n = 31). Correlations between iris characteristics and MPAs were expected, due to their same ectodermic origin. Iris macro photos were taken and quantified in five categories mentioned before. MPAs were also examined in both groups. Our results show significant differences in the frequency of pigment dots of the iris and total number of MPAs between groups. Other significant differences were found in the extension of concentric furrows, as they were more common in healthy subjects, while Wolfflin nodules occurred significantly more often in patients with schizophrenia. Expected difference in Fuch's crypts could not be observed between groups. Light eye color was positively correlated to pigment dots and Wolfflin nodules, and negatively correlated with concentric furrows. Dark eye color showed positive correlation with concentric furrows, and negative correlation with pigment dots and concentric furrows. A gender effect could also been observed: male individuals showed moderate positive correlations between pigment dots and total MPAs frequency, while this couldn't be observed in the female group. Our findings suggest possible connections between iris characteristics and MPAs, where males are more prone to deviations.

1. Introduction

1.1. Minor physical anomalies and schizophrenia

Minor physical anomalies (MPAs) are mild cosmetical errors of the skin which are results of insignificant errors of morphogenesis in prenatal stage (Pinsky, 1985). These MPAs could serve clinicians as a valuable indicator of altered morphogenesis in early gestation. Review of the literature gathered a significant amount of evidence demonstrating that people with neurodevelopmental disorders show elevated prevalence of MPAs compared to controls (Tényi et al., 2009). According to two meta-analysis numerous studies report an increased frequency of MPAs in schizophrenic groups compared to controls (Weinberg et al., 2007; Xu et al., 2011). There is also a possible hereditary factor. A recent study found that MPAs were more common in the head and mouth regions among the relatives of schizophrenia patients compared to normal controls (Hajnal et al., 2016).

1.2. Anterior cingulate cortex and schizophrenia

In recent decades we can see an increasing emphasis in cognitive neuroscience on a particular part of the limbic system, the anterior cingulate cortex (ACC). Earlier conceptions attributed a single function to this region: regulation of emotions. Subsequent studies have shown that the ACC's functions can be separated into two main parts. The anterior part is associated with emotion regulation and motoric functions, while the posterior part plays a role in visuospatial and memory processing (Bush et al., 2000). The cingulate cortex functions both as filter and amplifier, where the cognitive and affective components are linked together (Devinsky et al., 1995). The cingulate cortex plays an additional role in the regulation of attention and error control. It is possible that this area plays a role in disorders such as OCD, anxiety or excessive impulsivity if the ratio of emotional signal amplification is not appropriate (Bushet al., 2000). The ACC is also involved in pain perception. Lesions to this area reduce pain sensation. The patient is conscious of the painful stimuli, but it does not provoke a negative emotional reaction, and therefore it does not disturb him. (Folz and White, 1962). In regards to schizophrenia a meta-analysis of 7 studies showed reduced volume of the ACC in schizophrenia group compared to controls (Baiano et al., 2007), showing a neurodevelopemental background.

1.3. Human iris, PAX6 and the ACC

Studies confirm that Pax6 is a likely candidate gene for tissue differences in the iris. Pax6 dosage influence the muscle-cell differentiation in the iris (Jensen, 2005). Davis-Silberman et al. (2005) conclude that iris stroma defects are likely to be due to cell non-autonomous

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events, where Pax6 regulates the expression of the cells which are required for the adhesion of the iris stroma. Thus, it is possible that Pax6, Six3 and Lmx1b which influence the growth of the precursors to the cell layers in the iris, could influence the variability of crypts and contraction furrows typically present in peoples irises. The link between Pax6 and the anterior cingulate cortex has been already researched. One study demonstrated that family members with a mutation in Pax6showed high rates of unusual behavior, including disinhibition, impulsive behavior, impaired social understanding and impaired verbal inhibition (Heyman et al., 1999). A later study used magnetic resonance imaging (MRI) in this family (Ellison-Wright et al., 2004) and found local gray and white matter changes in the anterior cingulate cortex (approximate Brodmann area 24, 32), as well as posterior white matter abnormalities in the corpus callosum extending posteriorly into the cingulate cortex, which are brain areas that have been associated with personality traits (Davidson, 2001; Johnson et al., 1999; Posner and Rothbart, 1998).

1.4. Iris and personality

Larsson et al. (2007) pioneering study found significant correlations between iris structures and personality using the revised NEO personality inventory (NEO-PI-R), especially regarding to Fuchs crypts and concentric furrows. Larsson reported that people with many concentric furrows (also called nerve rings) were found to have a low ability to control impulses compared to people with few nerve rings. Results of Lim et al. (2014) show that psychological trait perseverance has a negative correlation with the grade of concentric furrows, which is consistent with Larsson's previous result. However, development of the concentric furrows not only has a negative correlation with perseverance, but also has a positive correlation with novelty seeking. Individuals high in novelty seeking tend to be excitable, exploratory, and easily bored, and those low in perseverance tend to give up easily when faced with frustration, criticism, obstacles, and fatigue. Although the above mentioned data are known on the connection between the iris structure and personality characteristics, no study was reported on the relationship between the iris characteristics and specific psychiatric disorders (schizophrenia, mood disorders, personality disorders).

1.5. The role of timing in the formation of iris structures

Fuch's crypts are patch like atrophies in the two top cell layers in the iris, the anterior border layer and underlying stroma. They are formed sometime between the third and eight month of gestation and are present at birth (Oyster, 1999). On the other hand, pigment dots can be rarely seen on the surface of the anterior border layer of the iris before the age of six (Eagle, 1988). Iris characteristics originating from the same cell layers generally share genetic factors. Examples are contraction furrows, which become manifest due to the iris folding in the same location when the iris aperture adapts to different light conditions. The overall thickness and density of the iris influence the extension and distinction of contraction furrows. Looking at iris color, the more pigmented iris also contributed to increased extension and distinction of contraction furrows, which indicated that the amount of melanin that is present in the iris increases its overall density (Larsson and Pedersen, 2004). A comprehensive recent study (Edwards et al., 2016) describes the distribution of the main iris features such as pigment spots, Fuchs' crypts, Wolfflin nodules or contraction furrows in large populations of European, East Asian and South Asian ancestry. After analyzing 1465 irises belonging to different people, the survey conclude that the distribution of iris features is very population dependent. They found that all traits showed significant differences in frequency across the three groups.

1.5.1. Four hypotheses were tested

First hypothesis was that both iris structures and MPAs are markers of neurodevelopment and there are significant differences between the schizophrenic and control group according to the frequency of Fuchs crypts, concentric furrows, Wolfflin nodules, pigment dots and minor physical anomalies. Theory behind the hypothesis is that a denser iris is expected more in healthy individuals, meaning low number of Fuchs crypts. While Fuchs crypts are regions with missing iris tissue, on the other hand contraction furrows are often results of the iris folding at the same spots when the pupil is expanding. Generally thicker irises are more prone to have visible folding marks. A higher number of Wolfflin collagen nodules and minor anomalies are expected in the schizophrenic group, mainly because of the same ectodermic origin of the iris, skin and central nervous system.

Second hypothesis assumed that there could be correlations between the frequencies of Fuchs crypts, concentric furrows, Wolfflin nodules, pigment dots and minor anomalies at the individual level. If there are significantly more crypts, nodules, pigment dots and minor anomalies in the schizophrenic group, there is a possibility that on an individual level we see aggregation of abnormalities.

Third hypothesis supposed that there will be a significant gender difference, where males are more likely to show deviation from average structural patterns, as other studies showed that iris characteristics are affected by gender (Lim et al., 2014).

Fourth hypothesis assumes positive correlations between lighter iris color and Wolfflin nodules and negative correlation with concentric furrows. Prior research suggests that Wolfflin nodules are more common in people with light eye color. It is also anticipated that darker irises are on average thicker than light colored ones and a thicker iris is more prone to folding, which causes concentric furrows.

2. Subjects and methods

The purpose of the study was to examine whether there is a quantifiable difference between the iris characteristics and minor physical anomalies of healthy and schizophrenia individuals in a Caucasian (Hungarian) sample. Macro iris photos of 31 healthy and 32 schizophrenic patients were used in the statistical analysis. The diagnosis of the schizophrenia patients were evaluated by the use of the DSM-5 (American Psychiatric Association, 2013). Patients with other neuropsychiatric disorders were excluded from the study, controls were healthy volunteers. No data on the family history of patients and healthy controls relating to psychoses were available. As we were interested in the correlations of the two trait markers (iris structure and MPAs), the evaluation of other clinical characteristics (positive and negative symptoms, age of onset) were not included in this study. Photos were taken from 30 cm distance with a 90 mm fix-focused macro lens. The structures were categorized with reference photos taken from Larsson's former study of iris structures and personality (Larsson and Pedersen, 2004). The examination of iris structures and MPA's were evaluated by two independent researchers. Before the statistical analyses inter-rater reliability was tested and the kappa coefficient was $> .75$ for all items. Iris structures examined in this study were Fuchs crypts, concentric furrows, Wolfflin nodules and pigment dots.

Regarding the examination of MPAs we have used the Méhes Scale for evaluation, which includes 57 minor signs (Méhes, 1988). Minor physical anomalies are connected to body regions for comparison and analysis of data. A clear differentiation between minor malformations and phenogenetic variants were introduced, the scale and detailed definitions were published earlier (Trixler et al., 1997, 2001; Tényi et al., 2004). All participants gave informed consent; the study was performed in accordance with the Declaration of Helsinki and was evaluated following institutional guidelines. The examination of minor physical anomalies was done qualitatively (present or absent) without scores being used, but where it was possible, measurements were taken with calipers and tape to improve the objectivity of examination. (Tényi et al., 2015).