# Iris structure and minor physical anomalies in schizophrenia

PhD thesis

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## Introduction

*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).

*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).

*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.

**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.

## 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 90mm fix-focused macro lens. The structures were categorized with reference photos taken from Larsson's former study of iris structures and personality (Larsson, 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 >0.75 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).

Figure 1. Examples of the studied iris structures. Different individuals' irises have been paired to demonstrate the two endpoints of the categorizing scale, from left to right: Fuch's crypts, pigment dots, concentric furrows, Wolfflin nodules..

**Statistics**

To examine mean differences between the two groups we used Mann-Whitney U test for ordinal scales (frequency of Fuchs Crypts, concentric furrows, Wolfflin nodules and pigment dots), for nominal scales Chi-square test were used (gender, eye color). To determine possible

correlations between iris structures and MPA's, Pearson's correlation test was initialized. The level of significance was determined as p=0,05 (2-tailed). Statistics were executed with IBM SPSS Statistics 22.

## Results

No significant differences were found in the mean age of the schizophrenia group (41) and the controls (37). Also no significant differences were observed when using Chi-Square test between the schizophrenic and control group regarding gender. $\chi^2(1) = 131.2$, $p = .244$.Male to female ratio in schizophrenic group was 20-12, control group 15-16.

### *Iris and MPAs*

Using Mann-Whitney test the frequency of Fuch's crypts between the two groups were not significantly different but regarding to the concentric furrows we saw a significant difference. We also observed significant difference in frequency of Wolfflin nodules. Pigment dots and MPAs, they were more common in patients with schizophrenia (see table 1.).

| | Schizophrenia (n=32) | Control (n=31) | Test of difference | Asymp. Significance (2-tailed) |
|---|---|---|---|---|
| | Mean Rank | Mean Rank | U | p |
| Fuch's crypts | 32.27 | 31.73 | 487.500 | .903 |
| concentric furrows | 27.63 | 36.52 | 356.000 | .047* |
| pigment dots | 36.64 | 27.21 | 347.500 | .041* |
| Wolfflin nodules | 36.16 | 27.71 | 363.000 | .039* |
| total MPAs | 44.09 | 19.52 | 109.000 | .000* |

Table 1. Differences in iris characteristics and MPAs between schizophrenia and control group.

*Effects of gender*

By splitting cases using gender only male patients showed significant differences using exact significance due to smaller sample size. Male subjects with schizophrenia showed significantly more pigment dots than the male controls. Concentric furrows were also significantly more common in the male control group.
By looking at the data of total MPAs, males with schizophrenia had higher numbers of total MPAs than the control male subjects. Females on the other hand showed only significant difference in the aspect of total MPAs between schizophrenic and control group (see table 2.).

| | Male Sch. (n=20) | Male Con. (n=15) | Test of difference | Exact Significance [2*(1-tailed)] |
|---|---|---|---|---|
| | Mean Rank | Mean Rank | U | p |
| Fuch's crypts | 16.53 | 19.97 | 120.500 | .330 |
| concentric furrows | 14.80 | 22.27 | 86.000 | .033* |
| pigment dots | 22.88 | 11.50 | 52.500 | .001* |
| Wolfflin nodules | 20.45 | 14.73 | 101.000 | .107* |
| total MPAs | 23.55 | 10.60 | 39.000 | .000* |
| | | | | |

| | Female Sch. (n=12) | Female Con. (n=16) | Test of difference | Exact Significance [2*(1-tailed)] |
|---|---|---|---|---|
| | Mean Rank | Mean Rank | U | p |
| Fuch's crypts | 16.17 | 13.25 | 76.000 | .328 |
| concentric furrows | 13.50 | 15.25 | 84.000 | .566 |
| pigment dots | 14.21 | 14.72 | 92.500 | .871 |
| Wolfflin nodules | 16.04 | 13.34 | 77.500 | .334 |
| total MPAs | 20.92 | 20.92 | 19.000 | .000* |

Table 2. Differences in iris characteristics and MPAs between schizophrenia and control group using gender as a subdivision.

*Effects of eye color*

Using eye color categories dark and light, the distribution in Mann-Whitney test revealed significant differences in pigment dots, concentric furrows and Wolfflin nodules. Darker eyed subjects had lower number of pigment dots. Results revealed also a lower rate of Wolfflin nodules in subjects with dark eye color. This is in correlation with prior studies which indicated that Wolfflin nodules are more common in lighter colored irises (Williams et al., 2011). It is noteworthy that while there was no difference using Chi-Square test in eye color between the two groups, there were more light eyed participants in the control group. *Schizophrenia group had 15 dark and 17 light eyed subjects, while the control group ratio was 12 dark and 19 light eyed.* Other finding was a higher rate of concentric furrows in dark eyed subjects, which supports the idea that darker irises with more layers of melanocytes are thicker and thus more prone to folding, which causes concentric furrows (Davidson et al., 2010). (see Table 3.)

| | Dark (n=27) | Light (n=36) | Test of difference | Asymp. Significance (2-tailed) |
|---|---|---|---|---|
| | Mean Rank | Mean Rank | U | p |

| | | | | |
|---|---|---|---|---|
| Fuch's crypts | 31.28 | 32.54 | 466.500 | .777 |
| concentric furrows | 44.39 | 22.71 | 151.500 | .000* |
| pigment dots | 25.13 | 37.15 | 300.500 | .010* |
| Wolfflin nodules | 26.31 | 36.26 | 332.500 | .016* |
| total MPAs | 34.41 | 30.19 | 421.000 | .356 |

Table 3. Differences in iris characteristics and MPAs between dark and light eye colored subjects regardless of mental status and original grouping criteria.

*Correlations*

By searching for correlations in the whole sample, we utilized Spearman's rank order correlation which demonstrated a weak negative correlation between concentric furrows and Wolfflin nodules ($r_s$ (63) = -.347, p =.005) and a near significant negative correlation between concentric furrows and pigment dots ($r_s$ (63) = -.238, p =.060). Expected correlations between iris categories and MPAs were only revealed by splitting all

cases using gender. Males showed moderate positive correlations between frequency of pigment dots and total minor anomalies ($r_s$ (63) = -.552, p =.001), while a significant difference could not been observed in the female group.

## Discussion

Regarding the first hypothesis, results revealed significant differences in the frequency of concentric furrows, Wolfflin nodules, pigment dots and total MPAs between the two groups. The expected difference was not significant when examining the frequency of Fuchs crypts. From Larsson's prior study we expected that we see most changes in Fuchs crypts which have the strongest genetic predisposition (Larsson et al., 2007). Interestingly we found differences rather in other iris characteristics: pigment dots, concentric furrows and Wolfflin nodules. Development of these nodules has not been linked to any brain region, so assumptions of differences was based merely on the ectodermic origin of the iris and the possibility that minor anomalies could be extended to this region also. This was supported by the results that schizophrenics had them significantly more often. We also found pigment dots more common in the schizophrenic group and found significant positive correlations between pigment dots and total minor anomalies, but only in male subject. This supports the third hypothesis that iris of males are more affected. Another difference was shown in concentric furrows. Healthy subjects had them more often and it negatively correlated

with frequency of Wolfflin nodules. A near significant negative correlation with number of pigment dots shows that a high number of concentric furrows could be indicator of a thicker iris with less pigment dots and Wolfflin nodules. Regarding eye color, we found similar results as prior studies in the aspect that Wolfflin nodules are more common in people with lighter eye color (Larsson et al., 2007; Davidson et. al, 2010). We also found that pigment dots were more common in people with light irises and concentric furrows were more common in participants with darker irises. Despite the schizophrenia group had fewer individuals with light eye color, we observed more pigment dots and Wolfflin nodules between them, which further reinforce the results of this study. It is important to point out that schizophrenia is a complex spectrum of conditions and is associated with many differences throughout the brain. It can be difficult to make specific links between brain areas and the symptoms that are often observed. A meta-analysis done by Glahn et al. (2008) found that patients had reduced gray matter density relative to control subjects in many regions, including bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus. Also some patients had increased gray matter density in striatal region. From these findings we can see that schizophrenia involves many brain regions not only the ACC, but the losses in the density of the iris have been only associated with the ACC so far, through the Pax6 gene expression.

A caveat of the study, that due to the relatively small sample, the effect of diagnosis, gender and eye color upon the studied variables (MPAs and iris characteristics) was

analyzed separately, multifactorial analysis could not be done because of the sample size.

**Conclusion**: To our knowledge this is the first ever study which examines the iris structural patterns of schizophrenia patients in relation to minor physical anomalies, compared to healthy controls. Results revealed significant differences in frequency of iris patterns and MPAs between the two groups. A gender effect could also be observed, both in iris structures and MPAs. This is in correlation with prior studies where males showed more MPAs (Sivkov and Akabaliev, 2003) and iris structural deviations (Lim et al., 2014). When looking for a higher frequency in Fuch's crypts, focus should be directed to mental health problems that are also linked to decreased tissue volume in the ACC, like impulse control disorders, where the diagnostic category doesn't show such a wide spectrum as in the case with schizophrenia. Our findings suggest concentric furrows, Wolfflin nodules and pigment dots could also serve as possible biomarkers. Because of the topics novelty the results indicate that there is potential and need for further research in this area, especially with a higher number of subjects.

## Publications

### Publications related to the thesis

Trixler D. 2013. Az emberi írisz mint lehetséges biomarker a személyiséghez. Psychiat Hungarica, 28 (2):199-206

Trixler D., Tényi T. 2017. Iris structure and minor physical anomalies in schizophrenia. Psychiatry Research, 256,412-416.

Impact factor: 2,223

### Abstracts related to the thesis

Trixler D., Tényi T. 2018. Irisz-struktúra és minor fizikális anomáliák szkizofréniában.Psychiatria Hungarica, 33, Suppl. 1, 134.

### Publications not related to the thesis

Tényi T.,Hajnal A., Halmai T., Herold R., Simon M.,Trixler D., Varga E.,Fekete S., Csábi Gy. 2014.

Minor fizikális anomáliák szkizofrén betegek hozzátartozói között. Szisztematikus áttekintő közlemény. Psychiatria Hungarica, 29,208-213.

Hajnal A., Tényi T.,Varga E., Simon M., Halmai T.,Németh N., Fekete S., Trixler D., Herold R. 2014. Szociális kognitív eltérések szkizofrén páciensek első fokú hozzátartozói között. Szisztematikus áttekintő közlemény. Psychiatria Hungarica, 29, 301-307

Hajnal A., Csábi Gy., Herold R., Jeges S., Halmai T., Trixler D., Simon M., Tóth Á.L., Tényi T. 2016. Minor physical anomalies are more common among the first-degree unaffected relatives of schizophrenia patients – Results with the Méhes Scale. Psychiatry Research,237, 224-228.

Impact factor: 2,528

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Impact factor: 2,223

Berecz H., Csábi Gy.,Herold R., Trixler D., Fekete J., Tényi T.2017. Minor physical anomalies and dermatoglyphic signs in affective disorders: A systematic review. Psychiatria Hungarica, 32,108-127.

**Abstracts not related to the thesis**

Hajnal A., Csábi Gy., Herold R., Jeges S., Halmai T., Trixler D., Simon M., Tóth Á.L., Tényi T. 2016. Minor fizikális anomáliák gyakoribb előfordulása szkizofrén páciensek egészséges elsőfokú hozzátartozóiban – Eredmények a Méhes-skálával. Psychiatria Hungarica, Suppl. 1., 64.

Berecz H., Csábi Gy., Jeges S., Herold R., Simon M., Fekete J.D., Trixler D., Hajnal A., Tóth Á.L., Tényi T.2018. Minor fizikális anomáliák előfordulása bipoláris I és bipoláris II zavarban –Eredmények a Méhes Skálával. Psychiatria Hungarica, 33, Suppl. 1., 15.

**Impact factor: 6,974**

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