Psychiatria Danubina, 2022; Vol. 34, No. 3, pp 431-438 https://doi.org/10.24869/psyd.2022.431 *Original paper*

INTERCONNECTION BETWEEN MIXED-HANDEDNESS, DIGIT RATIOS AND HAND AND FOOT MINOR ANOMALIES IN PREDICTING SCHIZOPHRENIA

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received: 14.1.2022; revised: 9.5.2022; accepted: 23.5.2022

SUMMARY

***Background**: According to the neurodevelopmental theory, brain structuring early markers could be seen in different body parts as minor physical anomalies. Alongside minor physical anomalies, handedness and index to ring finger ratio are brain development indicators, specifically brain lateralization. Studies are consentient about the association of these findings with schizophrenia, though there is inconsistency about individual anatomical regions' contribution. We proposed that handedness in combination with morphological indicators of early brain development could be sensitive and specific in predicting schizophrenia status.*

***Subjects and methods**: Within the list for the assessment of schizophrenia patients and normal controls of the Caucasian race were seven categorical minor physical anomalies of hand and feet, handedness, and index to ring finger ratio. In this cross-sectional study the examinees were recruited from January 2012 to December 2015.*

***Results**: Forced-entry binary logistic regression model correctly classified 86.5% of patients and 99.2% of the comparison subjects with a 92.8% overall accuracy. Mixed-handedness, hyperconvex fingernails, big gap between 1st and 2nd toe, and partial syndactyly of 2nd and 3rd toe made a significant independent contribution to the patient-control prediction group status. Furthermore, these items showed a significant correlation with the predictors of the head from the previous study.*

***Conclusion**: Briefly, the limb components, assessed independently of other body regions, proved to be worthy as schizophrenia predictors.*

***Key words:** neurodevelopmental markers - cerebral lateralization - atypical handedness - 2D:4D ratio*

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INTRODUCTION

Among several etiological theories of schizophrenia, the most persisting is the neurodevelopmental theory. Supported by a myriad of evidence, it utilizes minor physical anomalies (MPAs) as the subtle morphological deviations of different body parts, which are declared to be visual markers of intrauterine brain development (Lin et al. 2012, Weinberg et al. 2007). Nevertheless, the evidence varies significantly concerning these abnormalities' topographical distribution (Compton et al. 2011, Hajnal et al. 2016, Lin et al. 2012, Weinberg et al. 2007). A meta-analysis by Weinberg et al. (2007) suggests that anatomical regions do not differ from one to another in predicting schizophrenia with the help of MPAs, while some of the other authors indicate that the craniofacial section is more specific (Trixler et al. 2001). Some insist on hand region (Compton et al. 2007). This lack of consistency brings into existence more and more studies exploring the association of MPAs with not only schizophrenia but schizotypy, bipolar disorder, intellectual disability, and many other neurodevelopmental irregularities as well (Domany et al. 2018, Gooding et al. 2010, Kloiber et al. 2020, Mohamoud et al. 2018, Radua et al. 2018).

Besides MPAs, another way of explaining the etiology of schizophrenia is to capture abnormal cerebral lateralization (Barrantes-Vidal et al. 2013). Many studies report that handedness and index to ring finger ratio are potent indicators of atypical brain lateralization (Han et al. 2020, Qian et al. 2016, Tsuang et al. 2016). As for MPAs, the same pattern of indecisiveness could be seen in handedness results too. Mostly, studies document only mixed-handedness association with schizophrenia and other psychosis (Dragovic & Hammond 2005, Dragovic et al. 2005). Nevertheless, there are many data with only left-handedness or both mixed- and left- (non-right-handedness) being more frequent in patients (Barrantes-Vidal et al. 2013, Ravichandran et al. 2017, Tsuang et al. 2016). On the other hand, the 2nd to 4th digit (2D:4D) ratio correlates with testosterone level before birth, which disturbance can induce brain asymmetry, especially in the hippocampus region (Bolu et al. 2015, Han et al. 2020). The study of Stoyanov et al. (2009) demonstrates that the 2D:4D ratio is associated with handedness and explains that they could be used simultaneously as the cerebral lateralization indicators. Furthermore, some of the authors classify index to ring finger ratio as an MPA, making the classification of schizophrenia indicators more complex (Huang et al. 2010, Lin et al. 2012).

The approach of expanding the schizophrenia's phenotype by combining the MPAs with other possible markers like handedness, anatomical asymmetry, neurologic soft signs, and others is not novel (John et al. 2008, O'Callaghan et al. 1995, Reilly et al. 2001, Sommer et al. 2001). For instance, many years ago, O'Callaghan et al. (1995) put MPAs in juxtaposition with birth complications, family history, and handedness and discovered their mutual positive prognostic effect on schizophrenia. Still, there is a small number of studies dealing with only limb components. The usefulness of biomarkers conjunction is underpinned by the results of Reilly et al. (2001), where atypical handedness and hand dermatoglyphic fluctuating asymmetry together have indicated neurodevelopmental instability. Another proof comes from the study of Domany et al. (2018), which jointed deviations in the palmar creases, the shape of the fingers and nails with dermatoglyphic configurations in the palm in order to distinguish patients with schizophrenia from those with other mental disorders. They found investigated markers useful and specific and proposed them for application in clinical practice.

The present study aimed to investigate the association between the schizophrenia propensity and the combination of brain lateralization items and morphological features of limbs. Additionally, significant predictors found in this study were correlated with those for the head of the same patients published earlier.

SUBJECTS AND METHODS

Subjects

Patients with schizophrenia were recruited at the Clinical Center of Vojvodina in Novi Sad, Department of Psychiatry, from January 2012 to December 2015. All the patients satisfied the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for a diagnosis of schizophrenia (American Psychiatric Association 2013) based on case records review. The subjects were not assigned to a patients' group if they had a history of drug or alcohol abuse, a history of neurological disorders (seizures, multiple sclerosis, head trauma, and stroke), a clinically significant mental retardation, and illnesses/disorders that could have influenced finger/toe/limb length and shape. The mean length of illness since the first psychotic episode and the mean age of the first neuroleptic treatment were determined by reviewing patients' medical records. The group of patients with schizophrenia included 75 subjects with undifferentiated sub-type, 24 with paranoid sub-type, 24 with schizoaffective disorder, and three with disorganized sub-type.

The control group consisted of healthy comparison subjects (students, staff, and staff's relatives) recruited from the Faculty of Medicine, University of Novi Sad. All the volunteers were interviewed by a trained psychiatrist using Structured Clinical Interview for DSM-V non-patient version to ensure the absence of major mental disorders. All the subjects were of the Caucasian race. Migrants from other regions or states were excluded to avoid a geographical bias. Written informed consent was obtained from all the participants following a detailed explanation of the study procedures, with patient anonymity preserved. This cross-sectional study was approved by the Ethics Committee of the Clinical Center of Vojvodina and complied with the Helsinki Declaration.

Assessment and measuring

The presence of MPAs was assessed in areas of feet and hands using items from the Waldrop Physical Anomaly Scale: curved fifth finger (5^{th} finger clinodactyly), single transverse palmar crease, big gap between first and second toes, and partial syndactyly of second and third toe (Waldrop et al. 1968). We also assessed the following items not listed in the Waldrop Scale but found in the literature that could be associated with schizophrenia: hyperconvex fingernails, hyperconvex toenails (Ismail et al. 1998), 2D:4D ratio (Collinson et al. 2010), and handedness (Dane et al. 2009, Ravichandran et al. 2017). Further, we included the presence of the fifth toe clinodactyly.

Among investigated items, only the 2D:4D ratio was a continuous variable. Fingers' lengths were measured with the caliper on the palmar side, as the distance between midpoints of the bottom crease to the finger's tip, parallel to the longitudinal axis of the finger. The measurement was performed by a Vernier scale to the nearest 0.01 cm, being taken three times to make the average value. The results of the measurements were presented as ratios for both hands.

For the handedness assessment, we used the 4-item Edinburgh Handedness Inventory, a revised version made by Veale (2014). For the other categorical parameters, we assessed both the left and right sides of subjects and scored positive as either hand/foot was positive. The big gap between the first and second toe was considered the categorical variable. Namely, if the distance is equal to or exceeds the width of 0.60 cm, the big gap variable was scored positive (Sivkov et al. 2013). No objective standards were identified for the hyperconvex nails. Biesecker et al. (2009) described it as a tighter curve of convexity when viewed digit tip pointing toward the examiner's eye, and we used that definition. To reduce subjectivity, we scored subject positive if most of the nails of one of the hands/feet were hyperconvex (three or more from five fingers). Partial syndactyly of 2^{nd} and 3^{rd} toe was considered positive if the continuity of webbed toes is evident distal to flexion crease of the metacarpophalangeal joint regardless of length. A single transverse palmar crease was scored positive if the distal and proximal transverse palmar creases were merged. Curvatures of fingers/toes were defined as positive as the ones in the medial direction. We have noticed a frequent occurrence of the 5^{th} toe clinodactyly, with some subjects having overlapped

fourth and fifth toes and some with the 5th toe without being overlapped or overlapping the fourth toe. To include all the subjects in the analysis, we used the 5th toe clinodactyly term instead of overlapping toes, which meets the criteria found in Mohamoud et al. (2018). Considering that a person's gait, body weight, and various sports could be the factors leading to 5th toe clinodactyly, still not expected in adolescence or earlier (Boyer et al. 2014, Vulcano et al. 2013), we had asked subjects when they noticed it. Subjects have confirmed their toe has been like that since early childhood.

Assessment reliability

All assessments were performed by one of three trained anatomists, whose inter-rater reliability was examined before the recruitment of the examinees. Namely, inter-rater reliability was examined between three examiners, who co-examined 20 subjects independent of the current study groups. The Kappa values for the categorical parameters showed almost perfect agreement, with scores above 0.85 for every single item. The intraclass correlation coefficients for the continuous variables were measured using reliability analysis in SPSS, with scores above 0.82 for every single item. The examiners who evaluated MPAs were blinded towards diagnosis of a subject. Still, owing to the clinical setting of schizophrenia and the raters' medical background, it was challenging to avoid/limit bias, especially for the parameter like hyperconvex nails.

Statistical analysis

Two-tailed Fisher's exact probability or Pearson Chi-Square test with Yates' correction for continuity was used to compare categorical variables between two groups. For the comparison of continuous or ordinal variables, Student's t-test or Mann-Whitney U test was employed. Forced-entry binary logistic regression was used to determine which variables best discriminated patients from control group subjects. The specific items selected for the analysis with logistic regression were all the categorical variables with statistical significance of $p \leq 0.05$. The Woolf method with Haldane-Anscombe correction was used for the cells on the 2x2 table, where one of the cells' value was zero (Lawson 2004). The relationship between the group of discriminating variables found in the previous study for the head (Babović et al. 2019) and items found here was investigated using Pearson's product-moment or Spearman's rank order correlation. Preliminary analyses for the previously mentioned correlation tests were performed to check normality, linearity, and homoscedasticity. The IBM SPSS Statistics for Windows, version 23.0, was used for all the analyses (IBM Corp., Armonk, NY, USA).

RESULTS

Of 130 subjects with schizophrenia screened, 4 met the exclusion criteria and 126 were included in the study. The willingness to cooperate was satisfactory, so all of the included patients had finished study. Of 130 control subjects, 6 refused to participate when they were informed about study protocol leaving the final number of participants 124. The demographic characteristics of subjects could be found in Table 1. There was no significant difference in gender and age between the Patients and the Control group. The Patients group's age range was 19-63 years and 19-71 years for the control group. The Patients group's other features were the mean age of the first neuroleptic treatment (30.23±8.91 years) and the mean length of illness since the first psychotic episode (11.77±9.87 years).

Table 1. Demographic characteristics

Variables	Patients (*n*=126)	Control (*n*=124)	*p*
Male : Female	68 : 58	63 : 61	0.62
Age – years*	34.22±9.26	32.00±13.38	0.23
Range – years	19-63	19-71	/
Age of the first neuroleptic treatment – years*	30.23±8.91	/	/
Range – years	16-53	/	/
Length of illness since the first psychotic episode – years*	11.77±9.87	/	/
Range – years	0-36	/	/

* mean±SD

Table 2. Comparison of continuous variables between patients with schizophrenia and controls

Variables		Patients (n=126)	Control (n=124)	*t*	*p*
Right hand 2D:4D	all	0.982±0.042	0.988±0.052	1.07	0.29
	male	0.982±0.040	0.974±0.058	-0.93	0.35
	female	0.981±0.043	1.002±0.040	2.92	0.004
Left hand 2D:4D	all	0.998±0.044	1.002±0.038	0.66	0.51
	male	0.996±0.039	0.998±0.038	0.27	0.79
	female	1.005±0.048	1.000±0.039	0.70	0.48

Table 3. Comparison of categorical variables between patients with schizophrenia and controls

Variables		Patients (n=126) No. positive (%)*	Control (n=124) No. positive (%)*	*p*
Right hand dominant	all	100 (79.4)	110 (88.7)	0.070
	male	46 (79.3)	55 (87.3)	0.350
	female	54 (79.4)	55 (90.2)	0.150
Left hand dominant	all	5 (4.0)	11 (8.9)	0.180
	male	1 (1.7)	6 (9.5)	0.120
	female	4 (5.9)	5 (8.2)	0.740
Mixed-handedness	all	21 (16.6)	3 (2.4)	<0.001
	male	11 (19.0)	2 (3.2)	0.007
	female	10 (14.7)	1 (1.6)	0.010
Single trans. palmar crease	all	6 (4.8)	1 (0.8)	0.120
	male	2 (3.4)	0 (0)	0.230
	female	4 (5.9)	1 (1.6)	0.370
Curved 5th finger	all	23 (18.3)	4 (3.2)	0.001
	male	12 (20.7)	3 (4.8)	0.010
	female	11 (16.2)	1 (1.6)	0.005
Hyperconvex fingernails	all	45 (37.5)	0 (0)	<0.001
	male	25 (43.1)	0 (0)	<0.001
	female	20 (29.4)	0 (0)	<0.001
5th toe clinodactyly	all	21 (16.8)	2 (1.6)	<0.001
	male	6 (10.3)	1 (1.6)	0.060
	female	15 (22.4)	1 (1.6)	<0.001
Big gap between 1st and 2nd toe	all	44 (35.2)	0 (0)	<0.001
	male	26 (44.8)	0 (0)	<0.001
	female	18 (26.9)	0 (0)	<0.001
Part. syndactyly of 2nd and 3rd toe	all	49 (39.2)	23 (18.5)	0.001
	male	19 (32.8)	12 (19.0)	0.130
	female	30 (44.8)	11 (18.0)	0.002
Hyperconvex toenails	all	29 (23.2)	0 (0)	<0.001
	male	12 (20.7)	0 (0)	<0.001
	female	17 (25.4)	0 (0)	<0.001

* Percentage within a group of all, or only male, or only female subjects

The second to fourth finger ratios of both hands are shown in Table 2. All the comparisons were done between the Patients and the Control group only, not between sexes, nor between different hands. The second to fourth finger ratio was significantly lower for the right hand of females from the Patients group in comparison with the Control group (p=0.004). No significant differences for other comparisons of 2D:4D ratios were observed.

Seven categorical minor physical anomalies of limbs were compared. Besides MPAs, in Table 3 are presented results of handedness. Subjects of the Control and the Patients groups did not differ statistically regarding the left or the right dominant hand. In terms of handedness, there were significant differences in ambidexterity comparing all subjects together or divided by gender. The single transverse palmar crease was the only parameter that was not found different in opposed groups. Among the other hand items, curved 5th finger and hyperconvex fingernails were discovered more in patients than in normal control subjects. All the observed categorical MPAs of feet were present more in the Patients than in the Control group, with statistical significance reached in the comparison of all subjects. When subjects were stratified by gender, for 5th toe clinodactyly and partial syndactyly of 2nd and 3rd toe, statistical significance was lost in males.

Direct logistic regression was performed to assess the impact of several different items on the likelihood that subjects would be classified as patients or normal subjects. The univariate logistic regression foundseven independent variables to be statistically significant: mixed-handedness, curved 5th finger, hyperconvex fingernails, 5th toe clinodactyly, big gap between 1st and 2nd toe, partial syndactyly of 2nd and 3rd toe and hyperconvex toenails. The full model was statistically significant, χ^2 (4, N=250) = 232.84, p<0.001, indicating that it could distinguish patients and normal control subjects. Values of tolerance in collinearity diagnostics showed no significant multicollinearity between investigated predictors. Four investigated items made a significant ($p \leq 0.05$) independent contribution to predicting patient-

Table 4. Logistic regression model of discriminating patients with schizophrenia from controls

Variables	B	S.E.*	Wald	p	OR (95%CI)**
Mixed-handedness	-2.169	0.856	6.417	0.011	0.114 (0.021-0.612)
Hyperconvex fingernails	-4.754	1.086	19.145	<0.001	0.009 (0.001-0.72)
Big gap between 1st and 2nd toe	-4.992	1.086	21.140	<0.001	0.007 (0.001-0.057)
Partial syndactyly of 2nd and 3rd toe	-1.565	0.505	9.614	0.002	0.209 (0.078-0.562)

* Standard error; ** Odds ratio with 95% confidence interval

Table 5. Number of subjects (percentage within group) with discriminating items*

Group	0 items	1 item	2 items	3 items	4 items
Patients	8 (6.3)	30 (23.8)	49 (38.9)	34 (27.0)	5 (4.0)
Control	97 (78.2)	27 (21.8)	0 (0)	0 (0)	0 (0)

*p<0.001 Patients vs Control group

Table 6. Correlation of discriminating variables of the present study with the previously published results for discriminating variables of head

Variables	Hyperconvex fingernails	Big gap between toes	Partial syndactyly	Mixed-handedness
Two or more hair whorls	0.182**	0.109	0.181**	0.131*
Inner canthus distance	0.301**	0.127*	0.131*	0.187**
Outer canthus distance	0.220**	0.088	0.115	0.178**
Low seated ears#	0.288**	0.117	0.179**	0.252**
High-steepled palate	0.076	0.043	0.045	0.086
High flat palate	0.128*	0.136*	0.020	0.043

bottom of ears in line with mouth or lower; *p<0.05; **p<0.01

control group status, as presented in Table 4. According to this logistic regression model, significant predictors of schizophrenia are mixed-handedness, hyperconvex fingernails, big gap between 1st and 2nd toe, and partial syndactyly of 2nd and 3rd toe. The strongest single predictor was a big gap between 1st and 2nd toe with Wald's χ^2 value of 21.140. This model correctly classified 86.5% of patients and 99.2% of the comparison subjects with a 92.8% overall classification accuracy. Additionally, the results of Hosmer-Lemeshow goodness of fit test (χ^2=8.186; p=0.32) supported the model.

The differences in the number of discriminating items between patients and normal control subjects are demonstrated in Table 5. The Mann-Whitney U test (U = 1048.5, z = -12.44) showed a statistically significant difference (p<0.001) between the Patients and the Control group. There was no subject within the Control group with two or more discriminating items, while in the Patients group, there were 49 with two, 34 with three, and 5 with four items.

Tests for exploring the relationship between predictors from limbs with those from the previously published study demonstrated significant correlation (Table 6). Namely, the hyperconvex fingernails variable showed a correlation with almost all head MPAs; however, it reached significant medium-strength only with inner canthus distance (0.301, p<0.01). Big gap between 1st and 2nd toe, partial syndactyly of 2nd and 3rd toe, and mixed-handedness parameters significantly correlated with some of the head anomalies, still with small strength.

DISCUSSION

Although we did not conduct subjects matching, experimental groups did not differ significantly for age (p<0.23) and sex (p<0.62). In that way, the possibility of age and sex-related differences of morphological features and consequent bias is minimized; thus, this cross-sectional study is methodologically similar to that of Lin et al. (2012). Furthermore, results of the demographic characteristics showed that the mean length of illness (11.77±9.87) is much longer than for patients from the study of Collinson et al. (2010) (2.3±1.4 for males and 2.3±1.8 for females). Finally, one of the study limitations is that there is a possibility of other potential demographic differences between groups that could affect the results and were not investigated, e.g. educational background or living environmental factors.

We have considered some of the heterogeneous items connected to limbs, functionally or morphologically, as complex biomarkers for schizophrenia. Besides minor physical anomalies of hands and feet, the 2D:4D length ratio and handedness were also included in the analysis. Nevertheless, it is common for all of the investigated items to reflect the disturbance of brain development during gestation (Lin et al. 2012).

This cross-sectional study used the 2D:4D length ratio as a continuous variable, unlike some other studies which stated that transforming ratio into categorical variable might be more reliable and convenient (Huang et al. 2010, Lin et al. 2012). In this case, bias minimization was done with triple measurement of the same

subject's fingers and considering a mean value in the same manner as in the study of Qian et al. (2016). Unlike that study, we did not measure fingers from the photos of subjects' hands; instead, we used Vernier caliper to avoid measurement distortions (Collinson et al. 2010). Despite the differences, the results of all studies, including the present, are comparable. Our findings are entirely consistent with those of Huang et al. (2010), who found no significant difference when all patients with schizophrenia were compared to controls. However, with gender, stratification difference was evident for females. Venkatasubramanian et al. (2011) also reported that only in female patients with schizophrenia 2D:4D ratio is significantly decreased compared to controls. Still, there are studies with opposite results where male and female (Collinson et al. 2010, Han et al. 2020, Qian et al. 2016) or only male patients (Bolu et al. 2015) have significantly higher ratios. Even though most of the previously mentioned studies were done in Chinese ethnicity subjects, their controls possess the same dimorphism pattern in the 2D:4D ratio as in other ethnicities (Collinson et al. 2010). Unfortunately, in our study 2D:4D ratio did not reach statistical significance in univariate analysis therefore it was not included in the final regression model.

Apart from the 2D:4D ratio, handedness is another simple marker of brain lateralization. There is much evidence supporting mixed-handedness as a marker of neurodevelopmental disorders with atypical lateralization such as schizophrenia or schizotypy (Barrantes-Vidal et al. 2013). Our investigation led us to the same because results showed a statistically significant difference only for the mixed-handedness, regardless of gender. A higher number of patients was positive for the mixed-handedness than controls, which agrees with outcomes of the study of Dane et al. (2009). Furthermore, Ravichandran et al. (2017) demonstrated that non-right-handedness, classified as left or mixed handed, is elevated in schizophrenia and bipolar disorder. One of our and similar studies' main flaws is that forced right-handedness has to be taken into account. According to Tsuang et al. (2016), many mixed-handed are forced, right-handed persons. Namely, within the mixed-handedness group, forced had higher schizotypy scores than the unforced subgroup; however, both had higher scores than the non-mixed-handedness group.

Compton and Walker (2009) review article summarizes not so recent studies supporting MPA as a stable physical set that indicates neurodevelopmental abnormalities in both psychotic and affective disorders. A more recent umbrella review of risk factors found several to be associated with psychotic disorders. Among six highly suggestive class of evidence factors were MPAs and within a group of nine suggestive factors was non-right handedness, making them the good psychosis predictors (Radua et al. 2018). In our study, patients versus normal controls comparison of investigated limb MPAs and subsequent logistic regression analysis have further promoted the concept of phenotypic markers of schizophrenia. To further support results for predictors, we followed the methodology proposed by Hajnal et al. (2016). Similarly to their findings, our patients mostly had more than one discriminating item, and normal controls predominately had none. Except for a single transverse palmar crease, every other MPA (hyperconvex fingernails and toenails, curved 5^{th} finger, curled 5^{th} toe, big gap between 1^{st} and 2^{nd} toe, and partial syndactyly of 2^{nd} and 3^{rd} toe) was significantly more frequent in the group of patients regardless of gender. These findings are in contrast to the results of Huang et al. (2010), where the single transverse palmar crease was significantly more present in the patients' group; moreover, it was a significant predictor in their final regression model. Our final regression model showed that only three of the previously mentioned MPAs, together with mixed-handedness, are significant predictors of schizophrenia. Slightly better regression analysis results achieved MPA items than mixed-handedness, which is in concordance with the previously mentioned umbrella review (Radua et al. 2018). From those three MPA items, two were from the original Waldrop Scale (big gap between 1^{st} and 2^{nd} toe and partial syndactyly of 2^{nd} and 3^{rd} toe), and one was not (hyperconvex fingernails). In the study of Lin et al. (2012), partial syndactyly was excluded from further analysis because there were no subjects with it. However, a big gap between the first and second toe was found significant discriminating item. Tényi et al. (2015) explained that a big gap belongs to the phenogenetic variant subgroup of MPAs, still with a higher incidence in patients with schizophrenia. On the other hand, the study of Ismail et al. (1998) indicated that hyperconvex fingernails could also be a significant predictor of schizophrenia. When it comes to hyperconvex nails assessment, the issue of subjectivity becomes critical. According to Biesecker et al. (2009), no objective standard could be identified for the hyperconvex nails. As we stated in the Methods section, we tried to limit this study's weakness by increasing the number of positive fingers/toes. Not to forget to mention that hyperconvex toenails item, unlike fingernails, was not a significant predictor in the full model, although it had high significance ($p<0.001$) before multivariate logistic regression. The same pattern followed 5^{th} toe clinodactyly and curved 5^{th} finger.

Various attempts were made to discover the relationship between potential schizophrenia markers like MPAs, neurologic soft signs, obstetric complications, Positive and Negative Syndrome Scale scores, CNS structures, non-right handedness, and many others (Compton et al. 2011, Dean et al. 2006, John et al. 2008, O'Callaghan et al. 1995, Tényi et al. 2015). Despite that, we could not find articles dealing with the correlation between MPAs of different anatomical regions. Thus we put in relation the present study results and those for the

head of the same subjects that we used here. Our previous publication stated that inner canthus distances, outer canthus distances, two or more hair whorls, and high-steepled palate had the best discriminative power from the head items (Babović et al. 2019). Leaving aside the fact that mixed-handedness has functional implications on hand and does not belong to MPAs (Barrantes-Vidal et al. 2013), it could be said that all the markers linked to hands/feet correlated with head variables to some extent, with hyperconvex fingernails showing the best result.

CONCLUSION

Overall, handedness, a brain lateralization marker, and morphological features like a big gap between 1st and 2nd toe, partial syndactyly of 2nd and 3rd toe, and hyperconvex fingernails, when used in combination had respectable sensitivity and specificity in distinguishing schizophrenia patients from healthy controls. In addition, all markers found here correlated with those of the head to a certain degree. Thus, we demonstrated that set of items assessed on limbs only could be useful in predicting schizophrenia status.

Acknowledgements:

Prof. Lazar Velicki is kindly acknowledged for constructive comments, language editing, and proofreading.

Conflict of interest: None to declare.

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Sinisa S. Babovic: conceptualization, methodology, investigation, supervision, writing - original draft preparation, reviewing and editing.

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Sladjana Ralevic: methodology, investigation, resources.

Nebojsa P. Stilinovic: formal analysis, visualization, writing - original draft preparation, reviewing and editing.

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