

RELATIONS BETWEEN TWO BIOLOGICAL MARKERS OF ABERRANT NEURODEVELOPMENT – FOOT DOMINANCE AND MINOR PHYSICAL ANOMALIES

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Abstract

The aim of this study is to investigate the frequency of left foot dominance and minor physical anomalies (MPAs) in patients with schizophrenia and control subjects and to determine the relations between these two biological markers of neuronal dysontogenesis in schizophrenia.

A Combined Foot Dominance Scale consisting of two subscales – Chapman & Chapman Foot Dominance Subscale, supplemented with a new Complex Tasks Subscale, containing tasks for measuring spontaneity, precision, strength, and balance – and 7 MPAs were assessed in a sample of 180 subjects (98 schizophrenia patients and 82 controls). We introduced mean left-footedness as a new, more sensitive measure of left foot dominance in detecting a difference between subjects with schizophrenia and control subjects.

Left foot dominance is significantly higher in subjects with schizophrenia. Left foot dominance subjects are more often associated with MPAs. There is a significant positive correlation between left-footedness and MPAs.

Significant positive correlations between left-footedness and MPAs are an important additional evidence of the neuronal dysontogenesis in schizophrenia. The higher co-occurrence of two biological markers of dysontogenesis – left-footedness and MPAs – in one subject becomes a stronger reliable index of underlying aberrant neurodevelopment.

Key words: schizophrenia, dysontogenesis, foot dominance, Combined Foot Dominance Scale, minor physical anomalies, biological marker

Introduction. Lateralization is related to the preferred localization of a function or activity on one side of the body. Hand, foot, eye, ear dominance and linguistic lateralization are regarded as an expression of the functional asymmetry of the brain [1]. Footedness refers to the dominant or preferred foot in a context that necessitates choosing one of the feet for performing manipulative or mobilizing actions [2].

The neuroontogenetic theory of the etiology of schizophrenia states that the disorder is a consequence of aberrant brain development during the fetal or neonatal period. Shaping cerebral asymmetry is a key dimension of neurodevelopment. Lateralization of brain functions is at risk during early prenatal development. Abnormal hemispheric lateralization might underlie the genesis of schizophrenia and may play an important causal role in its psychopathology [3, 4]. Detectable abnormalities regarding cerebral lateralization indicate aberrant neurodevelopment.

Schizophrenia is associated with excessive left or mixed foot preference [5]. Some studies confirmed the excessive left or mixed preference for the three aspects of dominance – hand, foot, and eye – in schizophrenia patients vs. control subjects [6, 7]. Another study, however, could not confirm such a preference in patients with schizophrenia – neither for eye, nor for foot dominance [8].

Minor physical anomalies (MPAs) comprise a range of slight, clinically and cosmetically insignificant dysmorphic features representing subtle errors in the development of morphological structures in the region of the eyes, the ears, the mouth, the head, the hands, and the feet. Formed usually in the first and/or early second trimester, MPAs persist into adulthood. Since the body structures expressing MPAs typically have a coinciding prenatal development with the brain, the MPAs appear potentially valuable indices of disturbances in early neurodevelopment. They are found to correlate with changes in regional gray matter, including prefrontal cortex and basal ganglia. Alterations in these regions may have a role in the development of psychosis [9]. The consistently replicated higher frequency of MPAs in schizophrenia, supported by a meta-analysis [10], has been one of the mainstays of the neurodevelopmental model of this disorder [11, 12].

Methods. Subjects. The study was conducted in the Clinic of Psychiatry at “Alexandrovska” University Hospital in Sofia and at the State Psychiatric Hospital in Radnevo. The sample included 98 (56 men, 42 women) consecutively admitted schizophrenic inpatients with mean age 34.45 years ($SD = 15.67$, range 23–79) for men and 42.20 years ($SD = 11.38$, range 21–63) for women [13].

Instruments.

1. Modified Chapman & Chapman Subscale. Among the foot dominance instruments in the available literature, the most popular is the Chapman & Chapman questionnaire [2]. It includes 11 foot performed activities: Kick as high as possible, Kick a ball, Arrange cubes, Going through cubes with a ball, Rolling a golf ball around a circle, Stamp out a cigarette, Balancing a

rod on the thigh, Write your initials on the sand, Smooth the sand, Hopping on one foot, Tapping out a rhythm [13].

2. Complex Tasks Subscale. It includes four-foot dominance tests, measuring more complex tasks:

- Step up on a chair (assessing spontaneity);
- Pick up object with toe (assessing precision);
- Push shovel into the ground (assessing strength);
- Standing on one foot (preferred foot for carrying the body weight), (assessing balancing).

Measuring these additional complex tasks allows for a subtler and comprehensive assessment of foot dominance.

The Combined Foot Dominance Scale includes a total of 14 tasks, administered as performance assessments, not as preference questionnaires. Each test was performed twice and the subject was asked to perform the test again if there was any inconsistency in the preference.

Each foot test is rated: 0 – Preference of right foot; 1 – No preference (both feet equally); 2 – Preference of left foot. Each test score ranges from 0 to 2; the total score of the Combined Foot Dominance Scale ranges from 0 to 28.

The subjects were examined with a set of seven MPAs based on four items from the Waldrop Physical Anomaly Scale [14]: Transversally furrowed tongue, Adherent earlobes, Single transverse palmar crease, Curved fifth finger. The last three variables were separately assessed for the left and for the right side and thus overall 7 MPAs were assessed. The following modifications were made: the categories Adherent earlobes and Lower edges of the ears extending backwards/upwards (two grades of a single item in the original scale) were defined as separate items because of the high prevalence of the first and the occasional finding of the second. In the original scale Radially curved fifth finger (clinodactyly) is measured in three degrees: 0 – Norm; 1 – Slightly radially curved; 2 – Strongly radially curved. We measured it in only two degrees: 0 – Absent or 1 – Present, due to the vague definition of “slightly” and “strongly” and the low Cohen’s $\kappa < 0.60$ of clinodactyly in our reliability study [18]. Our acceptable level of reliability for concordance between categorical/ordinal scores was Cohen’s $\kappa > 0.75$.

Thus, the seven MPAs are scored qualitatively as 0 – Absent or 1 – Present. The score range for the MPA set is from 0 to 7.

The refusal rate of potential participants was insignificant (below 5%), excluding selectivity bias.

All assessments were performed by the same examiner (K.A.).

Statistical analysis. Data was analyzed with SPSS 25.0. Descriptive statistics, various non-parametric analyses were used. As our data is not continuous

and lacks normal distribution, the non-parametric Mann–Whitney test for means difference between two independent groups was used. Usually, the mean of a variable is more precise and sensitive to the difference between two groups than comparing the categories of the same variable.

Statistical significance was defined as $p < 0.05$; two-tailed.

Results. Mean left-footedness is higher for all foot tests, except Arrange cubes in schizophrenia patients vs. control subjects (Table 1). Schizophrenia patients have significantly higher mean left-footedness for Balancing a rod on the thigh (0.55 vs. 0.27, $p < 0.030$; over two times increase), Hopping on one foot (0.79 vs. 0.41, $p < 0.009$; nearly two times increase), Step up on a chair (0.87 vs.

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Comparison of mean left-footedness between schizophrenia patients and control subjects

	Schizophrenia (<i>n</i> = 98)		Controls (<i>n</i> = 82)		Statistical significance*	
	Mean	SD	Mean	SD	U	<i>p</i>
Chapman & Chapman Subscale						
Kick as high as possible	0.46	0.83	0.30	0.72	3678.5	0.165
Kick a ball	0.32	0.73	0.23	0.62	3882.5	0.530
Arrange cubes	0.34	0.71	0.40	0.77	3827.5	0.661
Rolling a golf ball around a circle	0.36	0.77	0.20	0.60	3631.0	0.101
Stamp out a cigarette	0.27	0.69	0.17	0.56	3739.0	0.293
Balancing a rod on the thigh	0.55	0.89	0.27	0.67	3396.0	0.030
Write your initials on the sand	0.21	0.61	0.15	0.52	3858.0	0.486
Smooth the sand	0.40	0.80	0.24	0.64	3712.5	0.237
Hopping on one foot	0.79	0.98	0.41	0.77	3241.0	0.009
Tapping out a rhythm	0.45	0.83	0.24	0.64	3545.5	0.091
Subscale Mean Sum	4.10	5.08	2.50	4.67	2872.5	0.004
Complex Task Subscale						
Step up on a chair	0.87	1.00	0.43	0.82	3107.0	0.002
Pick up object with toe	0.42	0.81	0.27	0.65	3622.5	0.242
Push shovel into the ground	0.69	0.96	0.65	0.93	3930.0	0.758
Standing on one foot	0.73	0.88	0.63	0.85	3707.0	0.450
Subscale Mean Sum	2.63	2.20	1.98	2.18	3127.5	0.027
Combined Foot Dominance Scale Mean Sum	6.77	6.75	4.47	6.43	2728.0	0.002

*Mann–Whitney test

0.43, $p < 0.030$; two times increase). Importantly, the mean sum of the Chapman & Chapman subscale the Complex Task Subscale mean sum are markedly significantly higher in schizophrenia patients vs. control subjects (4.10 vs. 2.51, $p < 0.004$, over 1.6 times increase). This shows the strong overall left shift tendency for foot dominance in schizophrenia patients vs. control subjects.

All seven MPAs show higher frequencies in schizophrenia patients vs. control subjects. The greatest differences are found for Single transverse palmar crease of the left hand ($p < 0.002$), Transversally furrowed tongue ($p < 0.006$), Single transverse palmar crease of the right hand ($p < 0.054$). Importantly, the sum of the seven MPAs is strongly significantly higher ($p < 0.003$) in schizophrenic vs. control subjects.

To address the low internal consistency of the MPAs of the Waldrop Physical Anomaly Scale [15] and to capture more subtly and diversely the multiple correlations between left-footedness and MPAs, the seven MPAs were divided into three groups in descending order of their differentiating strength between schizophrenia patients and control subjects.

1. Sum 3 MPAs = Single transverse palmar crease of the left hand, Transversally furrowed tongue and Single transverse palmar crease of the right hand
2. Sum 5 MPAs = Sum 3 MPAs + left/right Adherent earlobes
3. Sum 7 MPAs = Sum 5 MPAs + left/right Curved fifth finger

The Spearman's rank correlation matrix between the sums of the Chapman & Chapman Subscale, the Complex Task Subscale, and the Combined Foot Dominance Scale, and the Sum 3 MPAs, Sum 5 MPAs, and Sum 7 MPAs shows entirely positive correlations between left-footedness and MPAs in our sample:

- All nine correlations between these sums are positive;
- Some correlations are strongly statistically significant at $p < 0.01$: *Chapman & Chapman Subscale* with *Sum 3 MPAs* ($p < 0.008$); *Combined Foot Dominance Scale* with *Sum 3 MPAs* ($p < 0.003$);
- Some correlations are statistically significant at $p < 0.05$: *Complex Task Subscale* with *Sum 3 MPAs* ($p < 0.019$);
- Some correlations approach statistical significance: *Chapman & Chapman Subscale* with *Sum 5 MPAs* ($p < 0.161$); *Combined Foot Dominance Scale* with *Sum 5 MPAs* ($p < 0.114$).

The analysis of the correlation matrix ascertains a strong trend that the more left-footed the schizophrenia patient is, the more he/she is associated with MPAs and vice versa.

Discussion. In scientific literature laterality is found to be mostly assessed by hand dominance, although hand dominance is influenced by much more factors than foot dominance in the context of the bio-psycho-socio-cultural model for the genesis of every normal or abnormal human function. For example, human societies are predominantly right sided; social conformity imposes the use of the right hand; appliances, devices and instruments are adapted to the right hand. In Bulgaria, during the communist regime (before 1990) left hand writing was under cultural pressure.

The relatively weaker cultural pressure on foot dominance allows its assessment as a more adequate instrument for investigating and comparing laterality among different countries and societies.

In the assessment of foot dominance we used a Combined Foot Dominance Scale, comprising of a Chapman & Chapman Subscale, and a Complex Task Subscale, the latter containing four tasks for measuring spontaneity, precision, strength, and balance. This was needed because some authors suggest that unlike handedness, which is unidimensional [16], footedness is two-dimensional, differentiating unskilled versus skilled movement tasks [17]. Measuring these additional complex tasks allows for a more subtle and comprehensive assessment of foot dominance.

Our data is consistent with previous findings of higher frequency of non-right-footedness in schizophrenia [18].

It should be emphasized that the cumulative mean sum of our Combined Foot Dominance Scale is strongly significantly higher in patients with schizophrenia vs. control subjects ($p < 0.002$). This confirms that left-footedness is a strong biological marker of schizophrenia, indicating hemispheric abnormal lateralization.

MPAs are biological markers of early dysontogenetic processes and they do not change in the course of the disease [10]. Seven minor physical anomalies were assessed and their correlations with left foot dominance were studied. Statistically significant, strong, positive correlation was found between left-footedness and MPAs. It is evident that the more left foot dominant the subject is, the more he/she is stigmatized with MPAs and vice versa. This correlation has not been reported in the available literature. Abnormal lateralization and minor physical anomalies result from prenatal disturbances in the first or second trimester of prenatal development. Therefore, disordered neuroontogenesis leads to impaired cerebral lateralization, which is considered a basis for the development of schizophrenia.

In our data we could correlate the impaired neuroontogenetic process, ascertained by association with MPAs, to the impaired cerebral lateralization measured by increased left foot dominance.

Although we assessed only a set of the numerous MPAs described in the literature, we consider the many significant positive correlations between left-footedness and MPAs in the correlation matrix an additional important proof of the neuronal dysontogenesis in schizophrenia.

On the continuum of neuroontogenetic disorders any single biological marker may indicate a possible neurodevelopmental disturbance. However, the higher coincidence of two biological markers of dysontogenesis – left footedness and MPAs – in one subject appears a stronger reliable index of underlying brain anomaly and of the consequential neuronal dysontogenesis in schizophrenia.

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