ABSTRACT

Objective: The aim was to investigate left foot dominance as a biological marker of neurodevelopmental disorder in schizophrenia.

Material and methods: The Chapman & Chapman Foot Dominance Scale, administered as performance assessments, not as preference questionnaire, was assessed in a sample of 180 subjects (98 schizophrenic patients and 82 controls). Multivariate Analysis of Variance (MANOVA), non-parametric and cluster analyses were used to analyze the data.

Results: Left foot dominance was significantly higher in schizophrenic patients in comparison to control subjects.

Conclusion: As hand dominance is influenced by cultural factors, footedness might be a better-suited candidate biomarker for motor brain lateralization. We propose foot dominance as a useful, reliable, and more culturally independent indicator of brain lateralization.

Keywords
Schizophrenia, Neurodevelopmental disorder, Foot dominance, Biological marker, Chapman & Chapman Foot Dominance Scale.

Introduction
Cerebral asymmetry is a unique feature of the human nervous system and might be related to the development and evolution of humans from earlier primates [1]. Lateralization of brain functions is at stake during the fetal stages of individual development, suggesting that cerebral asymmetry is a key dimension of nervous development. Hemispheric imbalance might underlie the genesis of psychosis [2]. Recent work also shows that some of the genes associated with asymmetry and schizophrenia are preferentially selected in human evolution [3].

Foot dominance like hand, eye and ear dominance demonstrates brain lateralization and functional asymmetry [4]. Footedness refers
to the dominant or preferred foot, when performing manipulative or mobilizing actions in a bilateral context [5-7].

Schizophrenia is associated with excessive left or mixed foot preference [8,9]. Other studies have assessed the three aspects of dominance – hand, foot, and eye – and have confirmed the excessive left or mixed preference for the three of them in schizophrenic vs control subjects [10,11]. One study, however, could not confirm such a preference in patients with schizophrenia – neither for eye, nor for foot dominance [12].

We applied 23 not overlapping tests from the most widely used scales for assessing handedness - the Edinburgh Handedness Inventory (EHI), the Annett Hand Preference Questionnaire (AHPQ), the Chapman and Chapman questionnaire, the Hand Preference Demonstration Test (HPDT). We added 7 additional hand tests for assessing spontaneity, which made for 30 tests overall. We did not find a statistically significant difference in left-handedness between schizophrenic and control subjects although we used a large number of tests, measuring the quality of performance, precision and spontaneity of the proximal (shoulder, arm, and forearm) and distal (wrist, palm, and fingers) part of the upper limb. That could be explained by the different influences on hand and foot dominance. Foot dominance is much less a subject of social influence and that makes it a better indicator of lateralization than hand dominance, which is strongly culturally influenced - the cultural pressure during the communist regime and the material world of appliances, devices, instruments, adapted to right-handed individuals [5,13-19].

Being not that much affected by cultural influences makes foot dominance a more objective indicator of brain lateralization. In this context, the aim of our study was to investigate left foot dominance as a biological marker of neuronal dysontogenesis in schizophrenic patients.

Material and methods
This study is part of a larger investigational project on the intriguing relations between six groups of markers of neuronal dysontogenesis – left-handedness, left-footedness, left-eyedness, minor physical anomalies, digit ratio and cognitive (attention and memory) deficit.

Subjects
The study was conducted at the Clinic of Psychiatry at the 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 44.50 years (SD = 10.73, range 23-67) for men and 42.20 years (SD = 11.38, range 21-63) for women.

The patients satisfied the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for a diagnosis of schizophrenia based on case records review, DSM-V based semi-structured interview and information obtained from relatives for a stronger validation of the diagnosis [20]. In order to enhance the homogeneity of the schizophrenic group, potential subjects were excluded if they had a history of drug or alcohol abuse, identifiable neurological disorder (seizure disorder, head injury, multiple sclerosis, etc.), any signs of intellectual disability or somatic disorder with neurological components. Exclusion criteria also included any previous or present lower limb disorders hampering the performance of foot tasks, any disease that affects balance or coordination and the use of medication influencing balance.

The control group consisted of 82 subjects (30 men, 52 women) with a mean age 34.70 years (SD =16.82, range 18-79) for men and 34.45 years (SD = 15.67, range 23-79) for women. Normality was defined as the absence of a previous or present psychiatric disorder. Control subjects satisfied exclusion criteria similar to those applied to schizophrenic patients. In addition, to better separate between the two groups, we implemented another exclusion criterion for controls - having a first-degree relative with a history of a psychotic disorder, major affective disorder or suicide.

In order to avoid potential confound due to ethnic and racial differences related to minor physical anomalies (MPAs) or lateralization, both schizophrenic patients and controls were of Bulgarian origin. Individuals were excluded if their parental or grandparental ethnic group was other than Bulgarian.

The Local Ethics Committee approved the study and all subjects gave written informed consent prior to participation, after having been provided the opportunity to be acquainted with all the information concerning the study and ask questions related to it.

Assessments
Chapman & Chapman Scale
Among the foot dominance instruments in the literature available to us, the most popular is the Chapman & Chapman questionnaire [5]. 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.

Two modifications were made to the subscale:
- The task “Tapping out a rhythm of Yankee Doodle”, due to the fact that this melody is unknown to Bulgarians, was reformulated to „Tapping out the rhythm of a favorite song“.
- The task “Going through cubes with a ball” was excluded due to poor informativeness. The participants (mainly schizophrenic patients) could not complete the task by choosing only one foot to lead the ball and used both feet. This led to the false overuse of the category “Both equally”, which however did not reflect the actual dominant foot of the subject for this task.

The modified Chapman & Chapman Foot Dominance Scale includes 10 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 was rated: 0 - Preference of right foot; 1 - No preference (both feet equally); 2 - Preference of left foot. Each test score ranged from 0 to 2; the total score of the Foot Dominance Scale ranged from 0 to 20.

The same examiner (K.A.) performed all assessments.

Statistical Analysis
The data were analyzed with SPSS 25.0.

Descriptive statistics, non-parametric equivalents of correlation coefficient and cluster analysis were used for analyzing the data.

Multivariate analysis of variance (MANOVA) was used for comparing differences between several dependent variables overall.

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

Results
Descriptive Statistics of the Ten-Foot Dominance Tests in Schizophrenic and Control Subjects
The schizophrenic means of left-footedness are higher than the control means for all the foot tests, except Arrange cubes (Table 1).

The cumulative mean sum of the 10 foot tests is strongly higher for schizophrenic patients in comparison to controls (4, 10 vs. 2, 51).

Table 1: Means and Standard deviation of Ten Foot Dominance Tests in Schizophrenic and Control Subjects.

<table>
<thead>
<tr>
<th>Chapman &amp; Chapman Foot Dominance Tests</th>
<th>Schizophrenia (n=94)</th>
<th>Controls (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kick as high as possible</td>
<td>.47 .84</td>
<td>.28 .69</td>
</tr>
<tr>
<td>Kick a ball</td>
<td>.31 .72</td>
<td>.21 .59</td>
</tr>
<tr>
<td>Arrange cubes</td>
<td>.35 .71</td>
<td>.38 .75</td>
</tr>
<tr>
<td>Rolling a golf ball around a circle</td>
<td>.35 .76</td>
<td>.17 .57</td>
</tr>
<tr>
<td>Stamp out a cigarette</td>
<td>.26 .67</td>
<td>.15 .53</td>
</tr>
<tr>
<td>Balancing a rod on the thigh</td>
<td>.54 .89</td>
<td>.27 .67</td>
</tr>
<tr>
<td>Write your initials on the sand</td>
<td>.19 .59</td>
<td>.15 .53</td>
</tr>
<tr>
<td>Smooth the sand</td>
<td>.36 .77</td>
<td>.23 .64</td>
</tr>
<tr>
<td>Hopping on one foot</td>
<td>.81 .98</td>
<td>.41 .77</td>
</tr>
<tr>
<td>Tapping out a rhythm</td>
<td>.45 .84</td>
<td>.25 .64</td>
</tr>
<tr>
<td>Sum of 10 items</td>
<td>4.10 5.08</td>
<td>2.51 4.67</td>
</tr>
</tbody>
</table>

Comparison of the Ten-Foot Dominance Tests as a Whole between Schizophrenic and Control Subjects
Multivariate Analysis of Variance (MANOVA) was used to study the effect of schizophrenia on the set of the 10 foot dominance tests. Although ANOVA could be separately computed for each foot test, this approach ignores the interrelations between the foot tests. Substantial information may be lost when the correlations (partial correlations) between the tests are ignored, while the MANOVA model takes into account only the „unique“ contribution of every foot test from the set, adjusting for the effects of the other foot tests on every foot test. In our MANOVA model the independent classification was the categories “schizophrenic patients and controls” and the set of multiple dependent variables – the ten foot dominance tests. For this model the Pillai’s trace, which is the most powerful and robust statistics for evaluating multivariate differences, is statistically significant (F=1.894; p=.049). This indicates a strong overall difference between schizophrenic and control subjects in the set of 10-foot dominance tests as a whole.

The univariate ANOVA statistics with classification variable “schizophrenia – controls” and dependent variable - every individual foot test - show differences in favor of schizophrenic patients vs. control subjects except for Arrange cubes. The significance levels for the univariate ANOVA statistics are not adjusted for the fact that several comparisons are being made, therefore they have to be used with caution. However, they can be used as indicating the individual contribution of every foot test to the overall statistical significance of the Sum/set of the ten-foot dominance tests in favor of schizophrenic vs. control subjects (Table 2).

The strongest contribution to the overall statistically significant difference between schizophrenic and control subjects in the set of 10 foot dominance tests as a whole is that of Hopping on one foot [F=9.282, p=.003], which is statistically significant at p<0.01. It is followed by Balancing a rod on the thigh [F=5.053, p=.026], statistically significant at p<0.05. They are followed by Tapping out a rhythm [F=3.060, p=.082], Rolling a golf ball around a circle [F=3.027, p=.084] and Kicking as high as possible [F=2.457, p=.119], which contributions approach statistical significance at p<0.05. Following, in descending order of small, not statistically significant contribution, come Smooth the sand [F=1.379, p=.242], Stamp out a cigarette [F=1.349, p=.247] and Kick a ball [F=.970, p=.326]. The smallest contribution to the overall statistically significant difference between schizophrenic and control subjects in the set of 10 foot dominance tests as a whole is that of Write your initials on the sand [F=.258, p=.612]. Arrange cubes is against the general trend, with slightly higher mean of Control subjects vs. Schizophrenic subjects (.40 vs .34), [F=.081, p=.776]. As this difference is very small, the test Arrange cubes very slightly decreases the overall statistically significant difference between schizophrenic and control subjects in the set of 10-foot dominance tests as a whole.

Cluster Analysis
The K-Means Cluster Analysis of the tests (valid cases) divides the sample into 2 groups (clusters) in the end cluster centers (Table 3).

One cluster center (cluster 1) has high values, while the other cluster center (cluster 2) has low values for left-footedness, from the ten-foot dominance tests. The cross-tabulation of group affiliation “Schizophrenics vs. Controls” and “Cluster 1 vs. Cluster 2” allocation (Table 4) distinguishes, with statistical significance approaching p<0.05, schizophrenic patients vs. controls (p=.081). The number of schizophrenic patients among the 26 subjects allocated to the cluster with high value of left-footedness (cluster 1) is more than twice the number of control subjects - 69.2% vs.
### Discussion

Foot dominance, like manual, is a demonstration of motor brain lateralization. Even though the most widely used way for assessing laterality is hand dominance, foot dominance is much less susceptible to the effects of social pressure [21]. Footedness is less influenced by cultural norms, social teaching or adapted to the right hand appliances, when compared to handedness, where, as we already mentioned, the influences of these factors have been repeatedly documented [5,22-24]. Therefore, footedness would be a better and unbiased indicator of brain lateralization in comparison to handedness.

All examined foot tests means (except for the opposite trend of only one test - Arrange cubes) as well as the cumulative mean show higher left foot dominance in schizophrenic patients versus controls. The five foot tests with the strongest contribution are Hopping on one foot, Balance rod, Tapping out rhythm, Rolling a circle and Kicking high. There is a left shift tendency for foot dominance in schizophrenic versus control subjects. In MANOVA model, the Pillai’s trace was statistically significant. This affirms our conclusion that left foot dominance is a strong biological marker for schizophrenia. Another advantage that contributed to these strong results was the application of performance assessments, not preference questionnaires.

Besides, it is always more satisfactory and convincing to prove a scientific fact by using several statistical methods. The three different statistics used (MANOVA, non-parametric equivalents of correlation coefficient, K-Means Cluster Analysis) showed that the ten-foot tests demonstrate statistically significantly that the number of schizophrenic patients with dominant left-footedness exceeds the number of control subjects with dominant left-footedness.

Our data is consistent with previous findings in the literature. Existing studies suggest that non-right-footedness plays a role for schizophrenia [25]. In adults, mixed-footedness is indicative of a higher load of schizotypal traits, for which neurodevelopmental instability is considered as one possible cause [26,27]. Disordered neuroontogenesis, which happens in the first or second trimester of fetal development, may lead to impaired cerebral lateralization. Premorbid left or mixed-footedness may indicate hemispheric abnormalities, related to psychosis and schizophrenia. Footedness is similar to handedness in left or mixed-footedness indicating disrupted hemispheric lateralization. Elias and Bryden argued that cerebral lateralization may actually relate more to footedness than to other lateral preferences [28].

Therefore, footedness might be a better-suited candidate biomarker to approximate brain lateralization. In relation to this, there is evidence on a primacy of footedness appearing at a first glance suggestive of evolutionary ‘postural control’ theories that consider footedness as primary to handedness with regard to cerebral lateralization [29].

### Table 2: Univariate ANOVA of Ten-Foot Dominance Tests between Schizophrenic and Control Subjects.

<table>
<thead>
<tr>
<th></th>
<th>Kick high</th>
<th>Kick a ball</th>
<th>Arrange cubes</th>
<th>Rolling a golf ball</th>
<th>Stamp out a cigarette</th>
<th>Balancing a rod</th>
<th>Write on the sand</th>
<th>Smooth the sand</th>
<th>Hopping on one foot</th>
<th>Tapping out a rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>1.46</td>
<td>1.38</td>
<td>1.27</td>
<td>1.50</td>
<td>1.08</td>
<td>1.85</td>
<td>1.15</td>
<td>1.46</td>
<td>1.31</td>
<td>1.31</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>.19</td>
<td>.07</td>
<td>.21</td>
<td>.05</td>
<td>.05</td>
<td>.17</td>
<td>.00</td>
<td>.10</td>
<td>.51</td>
<td>.19</td>
</tr>
</tbody>
</table>

### Table 3: End Cluster Centers.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=81)</th>
<th>Schizophrenia (n=94)</th>
<th>Statistical significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Cluster 1</td>
<td>8</td>
<td>9.9</td>
<td>18</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>73</td>
<td>90.1</td>
<td>76</td>
</tr>
</tbody>
</table>

*χ² - Likelihood-ratio chi-square statistic

30.8% (18 vs. 8). However, the number of schizophrenic patients is almost equal to the number of control subjects (51.0% vs. 49.0%) among the 149 subjects allocated to the cluster with low values of left-footedness (cluster 2).
Authorship statement
All authors have made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

References